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Anxia Corda

Anxiety and related constructs as predictors and outcomes in the cardiac population

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Abstract

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This thesis comprises five studies investigating various aspects of anxiety and related psychological constructs in patients with myocardial infarction (MI), takotsubo syndrome (TS), and MI with non-obstructed coronary arteries (MINOCA).

In Study I, the factor structure and psychometric properties of the Swedish translation of the cardiac anxiety questionnaire were investigated, in a sample of post-MI patients. The dataset was split in two random halves and both exploratory and confirmatory factor analysis were conducted (EFA and CFA). These indicated that the questionnaire has acceptable psychometric properties but that there are some issues with its factor structure and validity that could be addressed.

In Study II, the associations between various aspects of anxiety and the risk of recurrent cardiovascular (CV) events were investigated, in post-MI patients. The physiological and behavioural, but not the cognitive and affective aspects of anxiety were related to the risk of recurrent CV events.

In Study III, short- and long-term effects of beta-blockers on symptoms of anxiety and depression were investigated, in post-MI patients. Patients randomised to taking beta-blockers had small increases in depressive symptoms but not in anxiety. Stratified analyses showed that patients that were taking beta-blockers prior to randomisaition were more susceptible to these effects.

Study IV was a systematic review of mental health status and quality of life (QoL) in patients after a MINOCA or TS. The risk of bias was high for a majority of the included studies (18/28). The existing evidence indicates that patients with MINOCA or TS experience worse mental health status and QoL than non-cardiac groups, and equal or worse than cardiac groups. Additionally, some studies indicate that reduced mental health status and QoL does not naturally improve over time.

In Study V, the effects of a patient-tailored ICBT for treating symptoms of stress and anxiety after a MINOCA or TS were investigated. The ICBT showed an effect on both symptoms of stress and anxiety for these patients, but the evidence to support that it could eliminate clinical levels of both stress and anxiety was weak. Sub-group analyses indicated that the treatment was effective for TS-patients but not for MINOCA-patients.

Keywords: Factor analysis, psychometric validation, cardiac anxiety, anxiety, depression, myocardial infarction, recurrent cardiac events, takotsubo syndrome, myocardial infarction with non-obstructed coronary arteries, ICBT

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List of Papers

This dissertation is based on the following papers, which are referred to in the text by their Roman numerals.

I. Leissner, P., Held, C., Rondung, E., & Olsson, E. M. G. (2022). The factor structure of the cardiac anxiety questionnaire, and validation in a post-MI population. *BMC Medical Research Methodology*, 22(1), 338.

II. Leissner, P., Held, C., Humphries, S., Rondung, E., & Olsson, E. M. G. (2024). Association of anxiety and recurrent cardiovascular events: investigating different aspects of anxiety. *European Journal of Cardiovascular Nursing*, 23(7), 720–727.

III. Leissner, P., Mars, K., Humphries, S., Karlström, P., Yndigegn, T., Jernberg, T., Hofmann, R., Held, C., & Olsson, E. M. G. (2024). Short- and long-term effects of beta-blockers on symptoms of anxiety and depression in patients with myocardial infarction and preserved left ventricular function: a pre-specified quality of life sub-study from the REDUCE-AMI trial. *European Heart Journal. Acute Cardiovascular Care*, 13(11), 789–797.

IV. Leissner, P., Olsson, E. M. G., Rondung, E., Sundelin, R., Spaak, J., Ulvenstam, A., Nordenskjöld, A., Kövamees, L., Lyngå, P., Held, C., Tornvall, P., & Humphries, S. (2025). Mental health status and quality-of-life after an acute myocardial infarction with non-obstructive coronary arteries or takotsubo syndrome: A systematic review. *European Journal of Preventive Cardiology*, *00*, 1–13.

V. *Leissner, P., *Sundelin, R., Rondung, E., Humphries, S., Held C., Spaak, J., Ulvenstam, A., Nordenskjöld, A., Norlund, F., Kövamees, L., Lyngå, P., Olsson, E.M.G., Tornvall, P (2025). Randomised controlled trial of internet-based cognitive behavioral therapy in myocardial infarction with non-obstructive coronary arteries or takotsubo syndrome. *Submitted to European Heart Journal.*

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*Equal scientific contribution

Contents

Abbreviations

ACS	Acute Coronary Syndrome
AHA	American Heart Association
AMI	Acute Myocardial Infarction
ANS	Autonomic Nervous System
BAI	Beck Anxiety Inventory
BADS-SF	Behavioural Activation for depression scale, short form
BMI	Body Mass Index
CA	Cardiac Anxiety
CAD	Coronary Artery Disease
CAQ	Cardiac Anxiety Questionnaire
CBT	Cognitive Behaviour Therapy
CFA	Confirmatory Factor Analysis
CFI	Comparative Fit Index
CHD	Coronary Heart Disease
CTT	Classical Test Theory
CV	Cardiovascular
CVD	Cardiovascular Disease
DSM	Diagnostic and Statistical Manual of Mental disorders
EFA	Exploratory Factor Analysis
e-SMINC	The E-health Treatment of Stress and Anxiety in Stockholm Myocardial Infarction with Non-obstructive Coronaries Study
HADS	Hospital Anxiety and Depression Scale
HPA	Hypothalamic-Pituitary Adrenal
HR	Hazard Ratio
ICBT	Internet-delivered Cognitive Behaviour Therapy
IHD	Ischaemic Heart Disease
KMO	Keyser-Meyer-Olkin
LMM	Linear Mixed Models
LVEF	Left Ventricular Ejection Fraction
MACE	Major Adverse Cardiac Event
MADRS-S	Montgomery-Åsberg Depression Rating Scale, self rated
MI	Myocardial Infarction
MINOCA	Myocardial Infarction with Non-Obstructive Coronary Arteries
MSIMI	Mental Stress Induced Myocardial Ischaemia
MTT	Modern Test Theory

PCL-C	Posttraumatic Checklist – Civilian version
PSS	Perceived Stress Scale
REDUCE	Randomised Evaluation of Decreased Usage of Beta-Blockers after Acute Myocardial Infarction
RQoL	REDUCE, Quality of Life substudy
SD	Standard Deviation
TLI	Tucker-Lewis Index
TS	Takotsubo Syndrome

Glossary

- **Acute Coronary Syndrome (ACS)** - A group of conditions caused by sudden, reduced blood flow to the heart, including unstable angina and myocardial infarction.
- **Acute Myocardial Infarction (AMI)** - Commonly known as a heart attack; occurs when blood flow to a part of the heart is blocked, causing tissue damage. Referring to the infarction currently happening or has happened very recently.
- **Autonomic Nervous System (ANS)** - The part of the nervous system that controls involuntary bodily functions, such as heart rate, digestion, and respiratory rate.
- **Coronary Artery Spasm (CAS) -** A sudden narrowing of the coronary arteries that can reduce or block blood flow to the heart, potentially causing chest pain or MI.
- **Coronary Artery Disease (CAD)** - Refers specifically to the build-up of atherosclerotic plaque in the coronary arteries, which reduces or blocks blood flow to the heart muscle. It is a major cause of angina, heart attack, and other cardiovascular complications.
- **Coronary Heart Disease (CHD) -** Refers to the clinical consequences of CAD, such as angina, myocardial infarction, or heart failure.
- **Coronary Microvascular Dysfunction (CMD) -** Impaired function of the small coronary arteries, which can cause chest pain and ischemia despite no blockages in major arteries.
- **Cardiovascular (CV) -** Relating to the heart and blood vessels.
- **Cardiovascular Disease (CVD) -** A general term for conditions affecting the heart and blood vessels, including CHD, stroke, and hypertension.
- **Epistemology -** The study of knowledge and how it is acquired. In research, it refers to the assumptions about how we come to know things and what counts as valid knowledge.
- **Hypothalamic-Pituitary-Adrenal (axis) (HPA-axis) -** A central stress response system involving interactions between the hypothalamus, pituitary gland, and adrenal glands.

- **Heart Rate Variability (HRV) -** The variation in time between heartbeats, often used as an indicator of autonomic nervous system function and stress.
- **Heart Failure (HF)** - A condition in which the heart cannot pump blood effectively to meet the body's needs. It often leads to symptoms like breathlessness, fatigue, and fluid buildup, and can result from various structural or functional heart problems.
- **Hypertension** - Also known as high blood pressure. It is a major risk factor for cardiovascular diseases, including stroke, myocardial infarction, heart failure, and kidney disease.
- **Ischaemic Heart Disease (IHD) -** Another term for CAD; caused by reduced blood supply to the heart muscle.
- **Left Ventricular Ejection Fraction (LVEF) -** A measure of how much blood the left ventricle pumps out with each contraction; used to assess heart function.
- **Major Adverse Cardiac Event (MACE) -** A composite endpoint in cardiac research that includes events such as heart attack, stroke, and cardiac death.
- **Myocardial Infarction (MI) -** Damage to heart muscle due to blocked blood supply; commonly referred to as a heart attack. Can refer to acute or chronic MI.
- **Myocardial Infarction with Non-Obstructive Coronary Arteries (MINOCA) -** A type of MI where coronary angiography does not reveal significant artery blockages; has varied underlying mechanisms.
- **Mental Stress Induced Myocardial Ischaemia (MSIMI) -** A temporary reduction in blood flow to the heart triggered by psychological or emotional stress.
- **Ontology -** A branch of philosophy concerned with the nature of being and reality. In research, it refers to assumptions about what exists or what can be known to exist in the world.
- **Spontaneous Coronary Artery Dissection (SCAD) -** A sudden tear in a coronary artery wall, which can lead to heart attack or sudden cardiac death, often affecting younger women.
- **Stroke** - A medical emergency that occurs when blood flow to a part of the brain is interrupted or reduced, preventing brain tissue from receiving oxygen and nutrients. This can be caused by a blocked artery or the rupture of a blood vessel.
- **Takotsubo Syndrome (TS) -** Also known as stress-induced cardiomyopathy or "broken heart syndrome"; characterized by transient heart dysfunction often triggered by emotional or physical stress.

Introduction

men were lords in riches... and that they yet, O yet, within the home, still had the anxious heart (anxia corda) which vexed life unpausingly with torments of the mind

Lucretius Carus, On the Nature of Things. 50 B.C.E

Cardiovascular Disease

A Short History

It has long been known that the function of the heart is to keep us alive. Already Galen, almost 2000 years ago, recognised that the heart had life-sustaining functions. In spite of the heart's central role in keeping us alive, it was not until quite recently that diseases of the heart had reached the epidemic proportions we see today. Still, in the early 20th century, infectious diseases, e.g., tuberculosis and pneumonia, were the leading causes of death (Jones et al., 2012). However, antibiotics were discovered, and together with improved hygiene and living standards, their mortality rates subsided. This led to longer life expectancies and cardiovascular disease (CVD) instead took their place (Dalen et al., 2014; Jones et al., 2012). By the mid-20th century, more than 1/3 of every death could be attributed to CVD, but still very little was known of its causes and, more importantly, how to prevent it (Mahmood et al., 2014).

A famous example is the death of the US president, Franklin D. Roosevelt, in 1945, who passed from a stroke caused by untreated hypertension (i.e., high blood pressure). Doctors at the time did not recognise the severity of his condition and his death shocked the public and medical community alike (Weintraub, 2023). In response to the growing concern about heart disease, the U.S. Public Health Service launched the Framingham Heart Study in 1948. This long-term, large-scale study aimed to identify the causes of CVD by tracking the health of residents in Framingham, Massachusetts. Eventually, the National Heart, Lung, and Blood Institute took over the Framingham Heart Study, and under its guidance the study became one of the most influential in medical history, identifying many of the key risk factors we know of today.

Epidemiology

While continuing advances in research have led to improved survival (Woodruff et al., 2024), CVD continues to be the leading cause of death world-wide, with the exception of the African Region (World Health Organization, 2020).

The biggest contributor to cardiovascular (CV) mortality is ischaemic heart disease (IHD) (World Health Organization, 2020), which may also be known as coronary artery disease (CAD) or coronary heart disease (CHD). These terms and abbreviations will be used according to the sources cited throughout this dissertation, but will all refer to the same condition. IHD refers to the build-up of stenoses, i.e., atherosclerotic plaques, in the blood vessels which leads to a narrowing or occlusion of the coronary arteries, which may cause cardiac ischaemia. Ischemia refers to the restriction of blood flow in some part of the body (e.g., the myocardium), leading to lack of oxygen supply in relation to the oxygen demand. A prolonged state of ischaemia in the myocardium may lead to myocardial cell necrosis and eventually death. When there is evidence of acute myocardial ischaemia along with at least one additional diagnostic marker, this is what is known as a myocardial infarction (MI) (Thygesen et al., 2018), colloquially known as a heart attack.

Several major studies and guidelines exist on what factors can predict the risk of CVD. The Framingham Heart Study found sex, age, diabetes, smoking, blood pressure, total cholesterol and high-density lipoprotein cholesterol as important risk factors (D’Agostino et al., 2008). Another major study, the INTERHEART study, identified nine lifestyle related risk factors associated with MI: abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, poor psychosocial factors, low consumption of fruits and vegetables, alcohol, and low regular physical activity (Yusuf et al., 2004). Contemporary guidelines on prevention of CVD state the main modifiable risk factors for IHD as blood lipoproteins, high blood pressure, cigarette smoking, diabetes and adiposity (Visseren et al., 2021).

Treatment and Prevention

Treatment and prevention of modifiable risk factors can be categorised at different levels depending on the stage of disease progression; the primordial level, primary level, secondary level and the tertiary level (World Heart Federation, 2025). The primordial level comprises national health policies, e.g., taxes and regulations regarding tobacco and sugar, and these interventions affect all individuals within a given society. In contrast, the primary, secondary, and tertiary levels instead consist of interventions focused on individuals. Both primary and secondary prevention aim to achieve lifestyle modifications, e.g., healthy diet, regular physical activity and smoking cessation, and to prescribe preventive medication. The difference between them being that primary is aimed at people with risk, but not yet developed CVD, while secondary is aimed at those with already developed CVD, at risk of recurrent events. The tertiary level consists of devices and surgery, applied in the later stages of disease progression. The later the intervention, the more costly and invasive, placing a greater burden on the individual and society (World Heart Federation, 2025). It is therefore in everyone's best interest to intervene as early as possible.

One of the most commonly used drug classes for secondary prevention after an acute MI (AMI) is beta-blockers (Vrints et al., 2024). Since their introduction in the 1960's, beta-blockers have constituted a fundamental part in the treatment of CVD. They act by blocking beta-adrenergic receptors and can effectively reduce blood pressure and help prevent recurrent CV events. However, recent findings indicate that beta-blockers may not offer any benefit in MI-patients with preserved left ventricular ejection fraction (LVEF) (Yndigegn et al., 2024). This, together with the many reported side effects, such as depression, insomnia and sexual dysfunction (Ko et al., 2002; Riemer et al., 2021), has raised the question regarding relevance of routine prescription of beta-blockers for patients with preserved LVEF.

Myocardial Infarction Without Significant Stenosis and Takotsubo Syndrome

Some patients are affected by a CV event, much similar to an MI, but with non-significant levels of coronary stenoses (< 50%). MI with non-obstructive coronary arteries (MINOCA) is a working diagnosis, used as an umbrella term, referring to a group of such ischaemic conditions (Thygesen et al., 2018). Currently, prevalence rates of MINOCA range between 5-15% of AMI cases (Fatade et al., 2024). Despite the absence of major stenoses, patients with MINOCA exhibit clear signs of myocardial injury, such as elevated cardiac biomarkers and ischaemic ECG changes. Table 1 summarises some of the key features of MINOCA (Abdu et al., 2020; Fatade et al., 2024).

Table 1
Key features of MINOCA

- Heterogeneous aetiology: includes plaque disruption, coronary artery spasm, spontaneous coronary artery dissection, coronary microvascular dysfunction, and coronary thromboembolism.
- More common in women and younger patients compared to myocardial infarction with obstructive coronary artery disease.
- Less likely to have traditional risk factors for cardiovascular disease, such as abnormal lipids.
- Often associated with emotional or physical stress.
- Exclusion of non-ischemic causes (e.g., Takotsubo Syndrome).

Takotsubo Syndrome (TS) is similar to MINOCA in some ways, but is not included under the umbrella as the diagnosis is not classified as an ischaemic process (Thygesen et al., 2018). Similar to MINOCA, TS share the characteristic of often being triggered by emotional or physical stressors (Templin et al., 2015). Table 2 summarises some of the key features of TS (Singh et al., 2022).

Table 2
Key features of TS

- Predominantly affects postmenopausal women, on average younger than MI patients with obstructive coronary artery disease.
- Presents with chest pain, ECG changes, and elevated troponins, similar to MI.
- Classic imaging shows apical ballooning of the left ventricle with hyperkinetic basal segments.
- Pathophysiology is not fully understood, but catecholamine-induced myocardial stunning is a leading theory.
- Though initially considered benign, TS is now recognized to carry significant morbidity and mortality, including risk of recurrence and long-term cardiac dysfunction.

While TS is distinguished from MINOCA, it may still be related, as for example coronary microvascular dysfunction has been proposed is a potential cause for TS (Crea et al., 2014), and that coronary artery dissection and TS commonly co-occurr as they have similar aetiologies (Y-Hassan, 2018). Although some patterns seem to emerge regarding patient characteristics, more research is needed to clarify these intricate relationships.

It has also been noted that patients diagnosed with MINOCA or TS have a higher prevalence of anxiety disorders, mental stress and other psycho-emotional characteristics compared with patients suffering from MI-CAD (Pais et al., 2018; Templin et al., 2015). Comparisons between MINOCA and TS are few, but one study found that while TS was associated with more in-hospital complications and psychiatric disorders, it was also associated with better long-term disease prognosis than MINOCA (Commeau et al., 2022).

Currently, there are no clear recommendations of how to support or treat patients with MINOCA or TS (Fatade et al., 2024; Lisci et al., 2025), a major concern for those affected regarding both their mental and physical quality of life (QoL).

Anxiety

Etymology

From the Oxford English Dictionary:

> < (i) Middle French *anxieté* worry, disquiet (late 12th cent. in Old French; French *anxiété*),
>
> and its etymon (ii) classical Latin *anxietāt-*, *anxietās* worry, solicitude, extreme care, over-carefulness, in post-classical Latin also discomfort in the chest (1559 or earlier) < (i) (Oxford English Dictionary, 2025a)

Definition

To understand anxiety is to take it in its historical and cultural context. As stated by psychiatrist Donald Klein, the understanding of anxiety has not followed a continuous cumulative development, but rather a series of zigzags in perspective (D. F. Klein, 2002). As such, understandings of the cause, the meaning of and importance of anxiety is not fixed in time, but depends on the dominating theoretical and cultural paradigm.

From early psychoanalytic traditions to contemporary psychiatric classification systems, anxiety has consistently been seen as a signal of internal or external threat. In psychodynamic theory, anxiety arises from unconscious inner conflicts, relating to threats to individual safety and interpersonal relationships (Freud, 1936, 1955, 1989). It is a danger signal from the unconscious, with the purpose of avoiding threats to the safety and security of the individual. The danger signal would trigger defences – behaviours with the purpose reducing anxiety – which would lead to suffering when they became too rigid or inflexible. In the focus of psychoanalysis and psychodynamic therapy, anxiety is not the direct focus of treatment, but by resolving unconscious conflicts and restructuring defences, it would diminish as a consequence.

In contrast, behaviourist approaches, marked by positivism and empirical experiments; anxiety here is seen as the response to a conditioned stimulus (Estes & Skinner, 1941). The feeling is in itself not serving a purpose but is like the behavioural response, a reaction to a conditioned stimulus (Friman et al., 1998). In other words, Skinner argued that there is no functional significance for the feeling of anxiety in behaviour analysis (Skinner, 1965). The conditioning of a stimulus occurs when a previously unconditioned stimulus is paired with an unpleasant experience (Estes & Skinner, 1941). Anxiety is then maintained and perpetuated by avoidance and escape behaviours, which prevent any further learning regarding the conditioned stimuli and responses (Krypotos et al., 2015). Therapeutic interventions like exposure and response prevention aim to break this cycle, not by exploring unconscious conflicts, but by replacing the conditioned associations through inhibitory learning (Craske et al., 2014; Helbig-Lang & Petermann, 2010; Krypotos et al., 2015).

The cognitive revolution reframed anxiety once again, emphasizing the role of thought patterns and interpretations. Aaron T. Beck, initially trained as a psychoanalyst, developed the cognitive theory of psychology based on studies of depression. In his studies he found that depression was caused by negative automatic thoughts, instead of internalised anger (as posited by psychodynamic theory) (Beck, 1961). Continuing on this theory, he proposed that also anxiety was generated by threatening automatic thoughts and images and that it was perpetuated by maladaptive cognitive processes (Beck et al., 2005). Beck also made a point of describing anxiety with different subsystems: affective, physiological, cognitive and behavioural, and symptoms respectively belonging to each (Beck et al., 2005). Treatment involves restructuring maladaptive beliefs and training attentional control, thereby directly targeting the mechanisms that perpetuate anxious states.

Contemporary psychiatric frameworks, particularly as outlined in successive editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM), reflect an evolving classification of anxiety. The 1st and 2nd versions were influenced by psychodynamic thought, viewing anxiety as central to many forms of psychopathology. However, with the 3rd edition in 1980, anxiety was redefined less as an explanatory process and more as a distinct symptom cluster, leading to the separation of anxiety and mood disorders (Crocq, 2015). Despite this shift, comorbidity rates have been high (Demyttenaere & Heirman, 2020), and more integrative diagnostic categories have been included in the later versions of the DSM, such as mixed anxiety-depression (American Psychiatric Association, 2013; Bell, 1994).

The contemporary definition of anxiety according to the American Psychological Association (APA) Dictionary of Psychology is:

> … an emotion … in which an individual anticipates impending danger, catastrophe, or misfortune. The body often mobilizes itself to meet the perceived threat … Anxiety may be distinguished from fear both conceptually and physiologically … Anxiety is considered a future-oriented, long-acting response broadly focused on a diffuse threat, whereas fear is an appropriate, present-oriented, and short-lived response to a clearly identifiable and specific threat. (American Psychological Association, 2025c)

The DSM-5 echoes this, and also adds a behavioural aspect:

> anxiety is anticipation of future threat… often associated with muscle tension and vigilance in preparation for future danger and cautious or avoidant behaviors. Sometimes the level of fear or anxiety is reduced by pervasive avoidance behaviors (American Psychiatric Association, 2013)

Consequently, there is variation in how anxiety is defined, whether by observable behaviours or by internal phenomena such as automatic cognitive processes or unconscious conflicts. Nonetheless, it is almost always considered a danger signal and is typically associated with physiological reactions, behavioural responses, and cognitive patterns that may lead to psychological suffering. Importantly, being a natural response to threat, anxiety is a normal emotional response and does not have to be pathological. It is when symptoms become too excessive or persistent that they may lead to clinical suffering.

Assessment

Primarily, anxiety symptoms are assessed in terms of factors such as the triggering stimuli, intensity, frequency and permanence. While these symptoms may have explanatory and predictive properties in their own right, they may also be interpreted based on certain criteria as psychiatric disorders. Typically, psychiatric disorders are only considered in terms of presence of clinical suffering, and serve as the basis for clinical decision making. Either considered as symptoms or disorders there are unique advantages and disadvantages to each approach.

The diagnosis of anxiety disorders is conducted through clinical interviews by mental health professionals, based on diagnostic manuals. In the DSM-5, anxiety disorders are defined by either the triggering stimuli (e.g., social situations or specific phobic objects) or by the intensity and permanence of symptoms (e.g., panic attacks or generalised anxiety) (American Psychiatric Association, 2013). Diagnoses of anxiety disorders are ideal for clinical decision making, to help answer questions like "should this individual be treated?" and "which treatment should this individual receive?" While necessary in a clinical context, conducting clinical diagnostic interviews are time-consuming and costly, and may not be feasible in a research context. Furthermore, although the intention of the latest versions of the DSM has been to foster scientific rigour, basing diagnoses on empirical evidence rather than theoretical assumptions, mental disorders are still descriptive, based on subjective judgement and semantics (Frances, 2013).

A more parsimonious way of assessing anxiety is by using questionnaires, consisting of a number of items reflecting the aspects of interest. Using questionnaires takes less time and can often be completed without the assistance of a professional. While these may not have the same diagnostic validity as clinical interviews, they are good for assessing perceived symptom levels. This means questionnaires are better at reflecting the true nature of anxiety, ranging from normal responses of threat to pathologically rigid. This is especially useful in research where you want to describe underlying processes and can use the flexibility and specificity of questionnaires. Furthermore, questionnaires also have clinical utility as they can speed up a screening process, assess progress and can also serve as a basis for discussion.

Another way of considering anxiety is by assessing associated biological markers (e.g., signs for activation of the autonomic nervous system; ANS). These markers are good for obtaining objective measures of psychosomatic processes and have even been incorporated in some forms of psychotherapy (Frank et al., 2010). However, due to cost and time consumption, it is difficult to administer on a larger scale. Furthermore, it may not always equal the subjective experience, as correlations with self-reported anxiety are usually only moderate (Roos et al., 2021). As such, the method of assessment should match the epistemological concept of interest.

When assessing anxiety there are many questionnaires available for use. Similar to the diagnoses of the DSM-5, they vary concerning triggers and temporality. Most of these questionnaires have been developed based on Classical Test Theory (CTT), using various methods to determine reliability and validity of the scales (Rose & Devine, 2014). This is an application of statistics and mathematics in human sciences, in an attempt to make parametric observations of unobservable constructs.

An underlying assumption of CTT is that any observed score in a questionnaire is a combination of both the "true score" and errors associated with the observed score (DeVellis, 2006). The strength of correlation between the observed score and the true score is what is defined as reliability. The standard way of assessing this correlation is by estimating α (Cronbach, 1951), which is a combination of the inter-relatedness of items and the length of the test, in the specific sample tested (Tavakol & Dennick, 2011). Because α improves with a higher number of items, higher reliability can be achieved by adding more items to the questionnaire, but this also makes the scale more inconvenient for administration. Thus, it is often ideal to construct a reliable scale but with as few items as possible (DeVellis, 2006). While α refers to the internal consistency of a test it should also reflect unidimensionality. However, in tests consisting of several factors α may not correctly reflect this property, and in these cases, it should only be reported for the individual factors (Tavakol & Dennick, 2011). To investigate the dimensionality of a scale within the CTT framework, factor analysis is the most common method (Costello & Osborne, 2005; DeVellis, 2006). Both exploratory factor analysis (EFA) and confirmatory factor analysis (CFA), can be used to investigate underlying factors of a scale (T. A. Brown, 2015; Joliffe & Morgan, 1992).

Other types of reliability tests are temporal stability (i.e., test-retest reliability) and interrater reliability. These are estimated by correlating scores between different times of assessment or between different judges of observations. The latter is only applicable to situations where the questionnaire is administered by a clinician (or another observer).

Validity refers to the extent that the scale actually captures the phenomenon of interest (Clark & Watson, 2016). Items to include in a questionnaire should be chosen deductively, based on theory, and confirmed empirically, by relating the construct to appropriate indicators for the construct in question (Bjelland et al., 2002; Cosco et al., 2012; Norton et al., 2013).

Relationship to Depression and Stress

Aside from anxiety, the most commonly reported mental health issues are depression and stress. While they are describing different mental health issues, there are similarities and overlap between them. Important note, there exists some ambiguity regarding term stress, whether it refers to a stimulus (stressor), or a subjective response (affective, behavioural, physiological, cognitive).

Anxiety and depression are frequently co-occurring. Comorbidity between generalised anxiety disorder (GAD) and mood disorders have been reported at around 50%, and over two thirds of patients with mood disorders have an anxious distress specifier (Demyttenaere & Heirman, 2020). Both types of disorders consist of symptoms that are partly defined by maladaptive cognitions and behaviours, and physiological reactions. It is reasonable that they either share common origin, or that one condition might cause the development of the other. The Tripartite Model of Anxiety and Depression posits that both anxiety and depression are part of a higher order factor, negative affectivity (Clark & Watson, 1991). In this model, anxiety is uniquely described by symptoms of physiological hyperarousal, and depression by symptoms of anhedonia. Anxiety and anhedonia have also been found to be temporally related, as individuals with anxious avoidance later develop depressive symptoms, mediated by anhedonia (Winer et al., 2017).

Stress as a response, is currently not primarily understood in terms of psychiatric disorders. There are some diagnoses in the DSM-5, under Trauma- and Stressor-Related Disorders, but these do not reflect the common experience of stress in everyday life. Therefore, comorbidity rates with anxiety are not reported in the same way as with depression, but rather as correlations when measured on a continuous scale. These studies are few, and perhaps considered unnecessary due to the considerable conceptual overlap. However, as an example, a study of nursing students *($n = 71$)* found that a measure of self-reported stress correlated with both state *($r = .51$)* and trait *($r = .65$)* anxiety (Kurebayashi et al., 2012).

Stress is defined by the APA Dictionary of Psychology as:

> the physiological or psychological response to internal or external stressors… influencing how people feel and behave… it may be manifested by palpitations, sweating, dry mouth, shortness of breath, fidgeting, accelerated speech, augmentation of negative emotions (if already being experienced), and longer duration of stress fatigue… By causing these mind–body changes, stress contributes directly to psychological and physiological disorder and disease… (American Psychological Association, 2025a)

An article on the APA website (American Psychological Association, 2025b) describes both anxiety and stress as emotional responses to stressful stimuli. They state that both symptoms of anxiety and stress may respond well to similar coping strategies, such as physical activity and a good sleeping hygiene. Additionally, the World Health Organization defines stress as "a state of worry or mental tension caused by a difficult situation" (World Health Organization, 2025), which is strikingly similar to the APA's definition of anxiety (American Psychological Association, 2025c). The definition of stress by APA also describes stress as a stimulus that could be a contributor to mental and physical disease. This conception is also the foundation of the stress-diathesis model, which posits that the development of psychological disorders is a result from a combination of diathesis (predisposition) and stressful life events (Monroe & Simons, 1991).

In conclusion, the terms of anxiety, depression and stress are complex and at times interchangeable. Sometimes they may refer to the same symptoms, e.g., physiological arousal in anxiety and stress, or different stages in a temporal process, e.g., anxious avoidance leading to anhedonic symptoms of depression. As such, focusing on specific symptoms may help avoid conceptual confusion and facilitate a more accurate understanding of phenomenon and their underlying processes.

Psychotherapy

Ever since the introduction of the "talking cure", psychotherapy has been a frequently occurring treatment for mental distress, and has been proven effective in treating a range of clinically relevant conditions (Shadish et al., 2000). When treating anxiety symptoms and disorders, various types of psychotherapy have been found effective; e.g., psychodynamic therapy (Leichsenring et al., 2023), cognitive-behavioural therapy (CBT) (Hofmann et al., 2012), systemic therapy (Pinquart et al., 2016), and metacognitive therapy (Normann & Morina, 2018).

Although many versions of psychotherapy exist, CBT has been considered the gold standard over the last decades (David et al., 2018). As the name CBT implies, it is a combination of both cognitive and behavioural therapeutic techniques, an integrative model built on different theoretical frameworks, often referred to as the three waves of CBT (Carona, 2022). The first two waves, behavioural therapy (BT) and cognitive therapy (CT), incorporate therapeutic techniques previously mentioned, with exposure and response prevention of BT and cognitive restructuring of CT. The third wave of CBT arrived about 20 years ago, introducing an increased focus on acceptance, value-driven action and mindfulness-based interventions (S. C. Hayes & Hofmann, 2017). Along with the third wave came a shift in focus from treatment protocols to processes of change, opening up for a more transdiagnostic treatment focus and inclusion of techniques from other theoretical paradigms (Fernández-Álvarez & Fernández-Álvarez, 2019; S. C. Hayes & Hofmann, 2017).

Just as there are different theoretical and philosophical paradigms and therapeutic techniques underlying CBT, the treatment can also be delivered in various ways. One such method that has been gaining increasing attention over the last 30 years is over the internet (ICBT). Many studies indicate that ICBT can be as effective as traditional face-to-face CBT (Andersson et al., 2019), and be especially useful for specific conditions and populations, where the content can be tailored to their specific concerns (Gratzer & Khalid-Khan, 2016). ICBT treatment programmes are based on the same principles as CBT but mainly consists of written text instead of oral communication. Both guided and un-guided treatment programmes exist, but the therapist-guided generally outperform the un-guided (Carlbring et al., 2018). The communication with the therapist can be either synchronous (in real time) or asynchronous (delayed or scheduled messages), where a combination of both is often pragmatic (Andersson & Titov, 2014).

Cardiovascular Disease and Anxiety

As research has continued to study risk factors for CVD, there has been an increased emphasis on psychosocial conditions – mainly stress, depression and anxiety (Levine et al., 2021). With the prevalence of anxiety disorders at about 20-40% in patients with CVD, they are a major concern (Celano et al., 2016; Lian et al., 2021). While for many these symptoms are transient, about half of those affected experience persisting concerns (Murphy et al., 2020). That some individuals improve over time and others do not, hardly comes as surprising, as other stressful life events, such as disasters, also give rise to mental and emotional distress that ameliorate over time (Krzysztof & Kaniasty, 2002). In these cases, emotional reactions and coping of the individual depends on both objective characteristics of the event (e.g., severity, duration, ambiguity) as well subjective appraisal (e.g., perception of risk or controllability) (Schwarzer & Schulz, 2003). It is likely that such objective and subjective factors also influence who experiences persisting mental health problems after their cardiac event.

In addition to the incidence of anxiety after a cardiac event, many studies seem to indicate that increased levels of anxiety also are associated with a higher risk of CVD and recurrent CV events. Already in the 1950's, Hans Selye posited that CVD would develop under long-term exposure to stress (Selye, 1956). Contemporary meta-analyses corroborate this hypothesis, showing that anxiety is related to both increased occurrences of CV events and CV death (Roest et al., 2010; Wen et al., 2021). However, there is not a complete consensus regarding this question, as conflicting findings from another meta-analysis failed to identify significant evidence of association with mortality, instead indicating that depression was a superior predictive variable (Celano et al., 2015). This is an important consideration, given the temporal and causal interrelations of anxiety and depression. If anxiety predicts both depressive symptoms and risk of recurrent CV events it would be a superior prognostic factor, but more research is needed.

It is also possible that the mixed findings regarding anxiety might be due to that different aspects of anxiety relate differently to the pathogenesis of CVD. For example, studies have found that when comparing various diagnoses and symptom clusters of anxiety, they related differently to the risk of morbidity and mortality (Martens et al., 2010; G. B. Parker et al., 2010; Roest et al., 2014; Van Beek et al., 2016).

Possible Pathways

The proposed mechanisms behind the association of anxiety and risk of CVD are usually categorised as behavioural and physiological (Celano et al., 2016; Levine et al., 2021).

The evidence for a behavioural pathway relies on the fact that many of the modifiable risk factors that are associated with CVD risk also have been found to relate to mental distress. Both unhealthy lifestyle behaviours (e.g., consuming fatty foods, being physically inactive, using tobacco and not following prescribed treatment plans), as well as the consequent disease markers (e.g., BMI, hypertension, hypercholesterolemia and diabetes) have been associated with stress and anxiety (Hert et al., 2018; Pedersen et al., 2017; Player & Peterson, 2011; Takagi et al., 2017).

The physiological pathway is hypothesised to be caused by various biological mechanisms that have been associated with both anxiety and stress and the pathogenesis of CVD, e.g., inflammatory response, reduced heart-rate variability, dysregulation of HPA-axis, dysfunction of the autonomic nervous system, altered serotonergic pathways and altered platelet aggregability (Celano et al., 2016; B. E. Cohen et al., 2015; Hert et al., 2018). This physiological pathway has for example been observed in studies of mental stress induced myocardial ischaemia (MSIMI) (Mehta et al., 2022). Evidence suggests MSIMI is different from ischaemia that is induced by exercise or drugs, and has shown to be an independent risk factor for CV death or recurrent MI (Vaccarino et al., 2021).

Beta-blockers

Additional to their use as secondary preventive medication for CVD, beta-blockers have been identified to have various neuropsychiatric effects (Keller & Frishman, 2003). As such, they have also been hypothesised to work as a treatment for anxiety, as they can reduce common symptoms such as tachycardia and an irregular heart-rate (P. E. Hayes & Schulz, 1987). The reduction of these symptoms could be anxiety-relieving in themselves, but could also help curb panic attacks which are commonly triggered by a racing heart. Additionally, beta-blockers may also have a long-term effect on anxiety, as they have been found to reduce emotional arousal in contextual fear conditioning (Grillon et al., 2004), which might make individuals more robust against developing anxiety. Early studies found them helpful, mainly to treat somatic anxiety, but less effective than benzodiazepines, that offer rapid and broad impact, also on the cognitive and emotional symptoms of anxiety (Domschke et al., 2010; P. E. Hayes & Schulz, 1987; Steenen et al., 2016). However, popularity of benzodiazepines has decreased, as they have been associated with many adverse risks, such as cognitive impairment, dependence, and abuse (Olfson et al., 2015). Furthermore, in patients with acute coronary syndrome (ACS), benzodiazepine use has been associated with an increased risk of PTSD (Von Känel et al., 2021). In this context, beta-blockers may represent a safer and more appropriate alternative, where they also confer cardioprotective benefits.

That said, beta-blockers are not without potential drawbacks. As previously mentioned, they have also been associated with psychological side effects, including depression, sexual dysfunction, and sleep disturbances (Ko et al., 2002; Riemer et al., 2021). These side effects may also impact anxiety negatively, for example sexual dysfunction may lead to performance anxiety (Pyke, 2020). Furthermore, the reduced physical capacity associated with beta-blockers, or the cognitive misattribution of reduced physiological responses may cause feelings of anhedonia. As previously mentioned, anhedonia is related to anxiety, as suggested by the tripartite model of anxiety and depression and mediation of anxious avoidance (Clark & Watson, 1991; Winer et al., 2017). Another potential long-term effect of beta-blockers may be hypothesised based on findings regarding benzodiazepines, that interferes with exposure therapy and impair the treatment effect on anxiety (Preston et al., 2025). While beta-blockers act through a different mechanism, their ANS-suppressing effects may similarly interfere with the emotional processing required for long-term therapeutic change.

These considerations highlight the importance of individualized treatment planning and careful monitoring when beta-blockers are used in populations vulnerable to both cardiovascular and psychological distress. It also remains to be seen whether short- and long-term effects of beta-blockers differ in relation to their immediate anxiolytic effects and their potentially prolonged interference with conditioning and exposure.

Cardiac Anxiety

During the 70's and 80's, psychiatrists in Germany noticed the frequent reporting of cardiac complaints in physically healthy individuals (Fiegenbaum, 1986; Harbauer-Raum, 1987; Maier et al., 1985; Nutzinger, 1987; Richter &

Beckmann, 1969). *Herzphobie,* or heart phobia, was then investigated as a subtype of panic disorder, defined by anxiety attacks and a catastrophic fear of heart malfunctioning. Continuing on the same subject, psychologist Georg Eifert conceptualised cardiophobia (Eifert, 1993), which he later called heart-focused anxiety (Eifert et al., 1996), and what is commonly referred to today as cardiac anxiety (CA). He abstained from restricting the condition to panic attacks, and allowed a more general description of worry and anxiety related to the functioning of the heart (Eifert et al., 2000). There is currently no clinical diagnosis, but it can be assessed in terms of symptom levels with the cardiac anxiety questionnaire (CAQ) (Eifert et al., 2000). The original study found that CA consists of three distinct components: fear of heart-related stimuli (CAQ-F), avoidance of activities that would stimulate the heart (CAQ-Av), and attention to heart-related stimuli (CAQ-Att).

Research on the reliability and validity of the CAQ has found that it is similar to, and likely to be predicted by, other self-reported measures of anxiety and anxiety disorders (Wedegärtner et al., 2020; White et al., 2010). A useful aspect of assessing CA is the factor structure of the CAQ, allowing the division of anxiety in emotional, behavioural and cognitive factors. This division allows a higher precision when differentiating symptoms of anxiety, and might be specifically helpful when investigating relationships to somatic health or for interventional design. For example, it has been found that while CAQ-Av, on the one hand, is related to more smoking and physical inactivity, CAQ-Att, on the other, is associated with less smoking and more physical activity (Hohls et al., 2020). This gives reason to believe that different CA aspects also relate to CVD prognosis in different ways. One previous study investigated the association between the risk of recurrent major adverse cardiovascular event (MACE) and CA (Van Beek et al., 2016). They found that overall, CA related to increased risk for MACE, but when investigating the subscales, only CAQ-Av was related to increased risk.

As the questionnaire has become widely used, it has been adopted and translated to several languages (Chiasson et al., 2019; Dragioti et al., 2011; Fischer et al., 2012; Inyoo et al., 2022; Israel et al., 2017; Marker et al., 2008; Sardinha et al., 2013a; Van Beek et al., 2012). In doing so, the factor structure has been re-evaluated and some variations have been found. It is therefore of interest to examine the factor structure of the CAQ and to compare the available factor solutions to easier judge the validity of the questionnaire. Furthermore the Swedish translation has not yet been investigated in terms of reliability and validity.

Psychological treatment for patients with CVD

Among patients with CVD, both psychotherapy and antidepressants, but also several other types of psychosocial care, have been found effective in treating symptoms of anxiety, depression and stress (Levine et al., 2021; Ski et al., 2024). Specifically, recent years have seen an increasing number of publications regarding the effect of ICBT on various psychological outcomes (Johansson et al., 2019; Mourad et al., 2022; Norlund et al., 2018; Särnholm et al., 2023). For example, nurse-guided ICBT for depression effectively reduced symptoms of depression and anxiety, in patients with CVD (Johansson et al., 2019; Westas et al., 2024). Focusing on specific cardiac disease groups, exposure-focused CBT was found effective for patients with atrial fibrillation (AF) in reducing symptoms of CA and depression, in reducing AF-specific health care consumption (Särnholm et al., 2023), and reducing symptoms of insomnia (Skúladóttir et al., 2024). Another study found no short-term effects of ICBT on symptoms of anxiety or depression (Norlund et al., 2018), but there was some evidence of a long-term benefit for CA (Humphries et al., 2021). This lack of short-term effects may be due to low treatment adherence (Wallert et al., 2018), which might in turn have been caused by the recruitment process. This trial was unique as it offered participation to post-MI patients during their hospitalisation, instead of using open advertisements. Although only patients with elevated anxiety or depression were included, mental distress improves spontaneously for many patients during the time following the event (Murphy et al., 2020). Although there might be great clinical benefit derived from offering treatment this early on, these findings highlight the need for careful screening and information when including patients to clinical trials of psychotherapy.

While the primary aim of psychological interventions is to improve mental health, their potential role in secondary prevention of CVD has also gained interest. However, in spite of the recognition of psychosocial factors as risk modifiers (Visseren et al., 2021), no convincing evidence of this have yet been established (Ski et al., 2024). Currently, studies are heterogenous, and although there is a trend towards a lower risk of all-cause mortality (risk ratio: 0.81, 95% CI: 0.39-1.69) and MACE (risk ratio: 1.22, 95% CI: 0.77-1.92), more studies are needed to arrive at a definite conclusion. Furthermore, there are several possible explanations why the evidence of secondary preventive effect of mental health interventions are lacking. For example, it is possible that because IHD develops over a long time, psychosocial interventions may be applied too late to have an effect. Another explanation could be that the relationship between CVD and psychosocial risk factors is spurious, a consequence of unknown confounding. Furthermore, it is also possible that some psychosocial interventions are better than others for the purpose of CVD prevention, and averaging study results hide this effect. There is for example one study that found an effect in reducing fatal and non-fatal CVD with group-based CBT focused on treating stress (Gulliksson et al., 2011). Finally, an issue with studies of psychosocial interventions is that they are often underpowered to detect differences in adverse events, and the lack of positive findings could simply be a methodological issue. As such, the potential benefit of psychological interventions on CV health remains a possibility, and more research is needed.

Evidence

> ...its etymon (ii) classical Latin ēvidentia quality of being manifest to the senses, quality of being evident to the mind, obviousness, that which is evident… (Oxford English Dictionary, 2025b)

Working in public health care in Sweden (and most Western societies) means following an evidence-based approach to medicine and psychology. That means following the best available evidence from data in systematic research (Sackett, 1997). Generated evidence in data could be interpreted and assessed according to the following essential qualities: 1) the measure of the strength of evidence, 2) the probability that a particular study design will generate misleading evidence, and 3) the probability that *observed* evidence is misleading (Blume, 2011).

As there are various approaches to statistics, in this dissertation, the generation and interpretation of evidence will be according to the frequentist approach. Ontologically, this approach refers to probability as an objective property, derived from observations in repeated experiments. Epistemologically, the standards of the frequentist approach have the goal of error avoidance, such as the probability of rejecting a true hypothesis or producing an interval that fails to cover the true value (Lin, 2024). This can be put in relation to the Bayesian approach where probability is defined as a more subjective degree of belief, and the standards are to output various degrees of belief. Bayesian methods have the advantages of being more intuitively interpreted and does not require as large sample sizes, while frequentist statistics are often seen as more objective and does not rely on prior information. While a case can be made for either approach, or even a combination of both (Bayarri & Berger, 2004), the frequentist has been applied in this dissertation, mainly because of familiarity with the methods and the standards of the field of medicine mostly relying on them for dissemination of knowledge.

Furthermore, p-values will be used and interpreted according to Fisher, as a measure of the strength of evidence (Fisher, 1970), and to serve as the basis of inductive inference (Fisher, 1935). This stands in contrast with the Neyman-Pearson approach of hypothesis testing, which instead serves to support inductive behaviour (Neyman & Pearson, 1933). This choice is motivated by the argument that a p-value should not alone serve as the basis of clinical decision making, but be complemented by effect sizes, confidence intervals and other contextual factors (Blume & Peipert, 2003). As a researcher, with this dissertation I do not intend to make a decision, but to measure the evidence pertaining to my research questions.

Research gaps

In summary, based on the current literature, several gaps in knowledge remain.

The Swedish translation of the CAQ has not yet been validated, and there is conflicting evidence regarding its factor structure.

The evidence of an association between anxiety and recurrent cardiac events indicates an association but there is conflicting evidence and replication studies are needed. Furthermore, there are indications that certain aspects of anxiety may relate differently to the risk of recurrent events, but these are largely unexplored.

Considering the use of beta-blockers in post-MI patients, there is limited knowledge of its potential side effects on anxiety and depression. They are established as effectively reducing symptoms of somatic anxiety in psychiatric patients, but little is known of this effect in cardiac groups. On the other hand, reports of psychiatric adverse events indicate that patients taking beta-blockers have a higher risk of depression. Finally, given the various neuropsychiatric effects of beta-blockers, it is not known whether the potential effects on anxiety and depression varies over time.

Emerging research on the conditions of MINOCA and TS indicate that they are suffering from impaired mental health status and QoL, but no clear synthesis of these results exist. Furthermore, while these patients have stated a need for mental health interventions, no empirical evidence supports the use of psychological interventions for MINOCA or Takotsubo syndrome, and there are no established treatment guidelines for their management.

Aims

The aim of this dissertation is to investigate how aspects of anxiety, and related psychological constructs, might be assessed, be used as prognostic markers, how they may manifest and how they can be treated after a cardiac event. More specifically, the aims are:

I. To investigate the factor structure and the psychometric properties of the Swedish translation of the cardiac anxiety questionnaire in a population of patients post myocardial infarction.
II. To investigate the association of anxiety with recurrent cardiac events in a population of patients post myocardial infarction, and the association between separate aspects of anxiety and recurrent cardiac events.
III. To investigate the short- and long-term effects of beta-blocker medication on anxiety and depression, in a population of patients post myocardial infarction with preserved left ventricular ejection fraction.
IV. To systematically review the existing evidence on mental health status and quality of life in patients with myocardial infarction with non-obstructive coronary arteries and takotsubo syndrome, after the acute event.
V. To examine the effectiveness of treating stress and anxiety in a population of patients post myocardial infarction with non-obstructive coronary arteries or takotsubo syndrome.

Ethical Considerations

All studies in this dissertation follow the ethical principles of working with human subjects, as declared in the Declaration of Helsinki. The data collected in the studies were handled in accordance with the General Data Protection Regulation (GDPR), and personal information of participants was protected by pseudonymisation. Data were stored securely on encrypted servers with access restricted to authorised research personnel only. Self-report questionnaires and clinical assessments were collected through a secure digital platform, and any paper-based materials were digitised and securely destroyed. Data will be retained for 10 years following study completion, in line with institutional guidelines of Uppsala University, and will be used solely for research purposes.

All participants provided written informed consent prior to enrolment in the studies. They were given detailed information about the studies' purposes, procedures, potential risks and benefits, confidentiality measures, and their right to withdraw at any time. The consent process ensured that participants had the opportunity to ask questions and received adequate time to consider their participation.

In Study V, given the psychological vulnerability of participants experiencing heightened levels of stress and anxiety, particular attention was paid to the monitoring and management of suicidality throughout the study. Suicidal ideation was assessed at multiple time points using validated self-report questionnaires administered at screening and on a weekly basis during the intervention period. Participants who indicated presence of suicidal thoughts were flagged, and automated messages were sent through the digital platform to the study group health care manager, the treating psychologist and the responsible researcher. In such cases, the psychologist conducted a structured follow-up assessment via telephone to determine the severity of risk and to ensure participant safety. If necessary, appropriate clinical referrals or emergency interventions were initiated in accordance with established ethical and clinical guidelines.

Methods

Overview of papers

Table 3

Overview of the five studies regarding study design, participants, type of data and analyses applied

Paper	Design	Participants	Data	Analyses
Paper I	Observational	930 post-MI patients	Standardised questionnaires	Confirmatory and Exploratory Factor Analysis
Paper II	Observational	935 post-MI patients	Standardised questionnaires, Registry Data	Cox Regression
Paper III	RCT	806 post-MI patients	Standardised questionnaires, Registry Data	Linear Mixed Models
Paper IV	Systematic Review	28 studies, MINOCA and/or Takotsubo patients	Standardised questionnaires, clinical interviews	Narrative synthesis
Paper V	RCT	88 MINOCA or Takotsubo patients	Standardised questionnaires, Registry Data	Multilevel Linear Regression

RCT: Randomised Controlled Trial, post-MI: post Myocardial Infarction, MINOCA: Myocardial Infarction without Obstructed Coronary Arteries.

Study design and participants

Study I and II

Participants of study I and study II were patients with a recent MI who were screened for participation in the U-CARE Heart Trial, investigating the effects of ICBT on anxiety and depression among patients recently diagnosed with an MI. The complete study design has been reported elsewhere (Norlund et al., 2018).

In short, the U-CARE Heart Trial recruited patients (age < 75 years) who had an MI within the last three months. Nine hundred and thirty-five patients were screened, and these constituted the basis for analyses in Study II, and the 930 patients that had complete scores on the CAQ were included in Study I.

Study III

Participants included in study III were a sub-sample of individuals who had consented to participating in the Randomised Evaluation of Decreased Usage of beta-bloCkErs (REDUCE-AMI) trial. The REDUCE-AMI was a multi-centre, registry-based, open label, pragmatic trial where participants were randomised to either receiving or not receiving beta-blocker treatment. These individuals were recruited within seven days of experiencing an MI and they had preserved LVEF (>50%). Specific inclusion criteria for the REDUCE-AMI have previously been reported (Yndigegn et al., 2023, 2024).

The sub-sample provided additional informed consent and completed additional questionnaires on QoL, anxiety, depression and sexual experiences which were followed-up at two time points (6-10 weeks and 12-14 months after MI).

Study IV

The review was pre-registered in the international Prospective Register of Systematic Reviews (PROSPERO 20202020 CRD42020160778), and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The Cochrane Library, CINAHL, PsychINFO, PubMed, ASSIA, Web of Science, Scopus and Embase were searched. The search terms included terms for exposure and outcomes, and based on Medical Subject Headings. Eligible criteria for inclusion were peer-reviewed studies, written in English, that included MINOCA- or TS-patients, assessed mental health status or QoL after the event, and used validated and standardised forms for mental health assessment. Studies following case study design were excluded. Two reviewers (PL & SH) independently conducted title and abstract screening, full-text screening and cross-referenced their decisions on inclusion and exclusion. The same two reviewers extracted data from included studies.

Study V

Participants of study V were patients participating in the E-health Treatment of Stress and Anxiety in Stockholm Myocardial Infarction with Non-obstructive Coronaries Study (e-SMINC), which was a randomised controlled trial of the effectiveness of an ICBT programme vs usual care, administered to patients recently diagnosed with Takotsubo or MINOCA. The study protocol is previously reported (Humphries et al., 2020).

Eligible study participants were patients admitted to a hospital in Stockholm, Örebro or Östersund with a suspected MINOCA or TS between November 2021 and November 2024. To be included, patients needed to have less than 50% stenosis, as confirmed by angiography, be over the age of 35, have proficient skills in the Swedish language and have access to and ability to use the internet. Patients were randomised to either the treatment arm, to receive ICBT immediately, or the control arm, who receive the ICBT after follow-up 1. Data on questionnaires of stress and anxiety was collected at baseline, follow-up 1 (3 months), follow-up 2 (6 months) and follow-up 3 (1 year).

Questionnaires

Table 4
Overview of questionnaires used in studies I, II, III and V.

	Study			
	I	**II**	**III**	**V**
Hospital anxiety and depression scale	X	X	X	X
Cardiac anxiety questionnaire	X	X	X	X
Post-traumatic symptoms checklist, civilian version	X			
Montgomery-Åsberg depression rating scale, self-rated	X			
Behavioural activation for depression scale, short form	X			
Perceived stress scale, 14 items				X
Impact of event scale, 6 items				X

Hospital anxiety and depression scale

The hospital anxiety and depression scale (HADS) was used to assess symptoms of anxiety and depression (Zigmond & Snaith, 1983). Comprising 14 items, the respondent is asked to rate the frequency and number of symptoms over the last week, with seven items describing symptoms of anxiety (HADS-A) and seven symptoms of depression (HADS-D). Items are graded on a response scale using five ordered categories; with varying category labels between items. The score can be summarised with a total score range of 0-42 or 0-21 per scale. In a systematic review, the internal consistency for HADS-A has been reported in the range of α=0.68-0.93 (mean α=0.83), and for HADS-D in the range of α=0.67-0.90 (mean α=0.82), and a cut-off of ≥8 on either HADS-A or HADS-D has shown sensitivity and specificity rates of 0.70 to 0.90 for detecting possible cases of anxiety (Bjelland et al., 2002).

Cardiac anxiety questionnaire

The CAQ was used to assess the frequency and number of symptoms of heart-related anxiety (Eifert et al., 2000). It consists of 18 items, rated on a response scale using five ordered categories; “never”, “rarely”, “sometimes”, “often”, "always". While a 3-factor structure, with CAQ-F (8 items), CAQ-Av (5 items), and CAQ-Att (5 items) is the most common (Eifert et al., 2000), a 4-factor structure has also been suggested, taking three items from CAQ-F to create a subscale called Reassurance Seeking (Chiasson et al., 2019; Israel et al., 2017; Marker et al., 2008; Van Beek et al., 2012). It has been suggested to divide the score of each subscale with the number of items, thus resulting in a total (CAQ-T) and subscale score range of 0-4 (Eifert et al., 2000). In the original article, internal consistency for the total scale was .83, and for each of the subscales (Fear α= 0.83; Avoidance, α=0.82; and Attention, α=0.69) (Eifert et al., 2000). The questionnaire has no empirically established cut-off values.

Post-Traumatic Symptoms Checklist, civilian version

Originally developed to assess and screen for posttraumatic stress disorder (PTSD), the PTSD checklist (PCL) has been adapted to both military (PCL-M) and civilian (PCL-C) populations (Weathers et al., 1993). The PCL-C was developed based on the DSM-III-TR version of PTSD and used to assess the number of and intensity of distress of PTSD symptoms. It consists of 17 items rated on a response scale of five ordered categories; "not at all", "a little bit", "moderately", "quite a bit", "extremely". Scores can either be reported as a total symptom severity score, or separate severity scores for each symptom cluster (Re-experiencing, Avoidance and Hyperarousal). In a systematic review, internal consistency has been estimated at α=0.94 for the full scale, α=0.86 for Re-experiencing, α=0.81 for Avoidance, and α=0.85 for Hyperarousal, and the optimal cut-off point for identifying PTSD was determined between 35 and 38 (Bressler et al., 2018). Being used in Study I, the participants were asked to answer the items based on the cardiac event as the trauma.

Montgomery-Åsberg depression rating scale, self-rated

The Montgomery-Åsberg depression rating scale, self-rated (MADRS-S) was used to assess the number and/or intensity of depressive symptoms (Montgomery & Asberg, 1979). It consists of 9 items, rated on a response scale of seven ordered categories, with varying labels based on the question. The total score range was 0-54. The internal consistency of the scale has been estimated at α=0.84, and it has shown a moderate correlation with the clinician-administered version (r=0.54) (Fantino & Moore, 2009).

Behavioural activation for depression scale, short-form

The behavioral activation for depression scale, short form, (BADS-SF) was used to assess escape and avoidance behaviour in depression (Manos et al., 2011). It consists of nine items, graded on a response scale of seven ordered categories; "not at all", "a little", "a lot", "completely". Factor analysis has shown that it can be divided in the two subscales Avoidance (3 items) and Activation (6 items). The total score ranges between 0-54, and 0-18 for Avoidance and 0-36 for Activation. Internal consistency was estimated at α=.776 in a community sample and at α=.844 in an undergraduate student sample (Manos et al., 2011).

Perceived stress scale, 14 items

The perceived stress scale, 14 items, (PSS-14) was used to assess the degree to which respondents find their lives unpredictable, uncontrollable, and overloading during the last month (S. Cohen et al., 1983). It consists of 14 items, graded on a response scale of five ordered categories, “never”, “almost never”, “sometimes”, “fairly often” and “very often”. The total score ranges between 0-56. Based on Swedish norms, a cut-off ≥ 25 has previously been used to discriminate between normal and heightened levels of stress (Brinkborg et al., 2011; Eskin & Parr, 1996). The PSS-14 may also be described by two the subscales, Coping and Distress (Rozental et al., 2023). In a systematic review, it was reported that internal consistency was above α=0.70 in 11 of 12 studies, and that test-retest reliability acceptable for intervals of < 4 weeks (Lee, 2012).

Impact of event scale, 6 items

The impact of event scale, 6 items (IES-6), is a short form of the revised, 22-item, impact of event scale (Thoresen et al., 2010), and was used to assess the intensity of subjective distress following a traumatic event. The 6 items are graded on a response scale of five ordered categories; “not at all”, “a little bit”, “moderately”, “quite a bit” and “extremely”. The total score ranges between 0-24. The 6-item version has demonstrated good internal consistency, a high correlation with the 22-item version, and has been proven stable across several subgroups and populations. A cut-off value of ≥ 9 has been shown to predict a clinically significant score on the PCL with 0.86 sensitivity and 0.88 specificity, in indicating post-traumatic stress disorder (PTSD) (Thoresen et al., 2010). Being used in Study V, the participants were asked to answer the items based on the cardiac event as the trauma.

Representation of phenomenological aspects

In this dissertation, the anxiety subscale of the HADS (HADS-A) and CAQ (total score and its subscales) represent different phenomenological aspects of anxiety. HADS-A is generally used to screen for generalised anxiety (Bjelland et al., 2002), but was chosen to represent physiological arousal. This is due to 6 out of the 7 items on the scale describing at least one component of this aspect. CAQ-F represents cognitive rumination and affective fear, CAQ-Av represents behavioural avoidance, CAQ-Att represents cognitive hypervigilance and CAQ-T represents a composite of the three CAQ subscales.

Although in Study I, a new and shorter version of CAQ was generated which might have been better, these findings need to be replicated before rejecting the original version which still was employed in the other studies.

Analyses

Stata Software Package was used to perform all statistical analyses except calculations of absolute risks in Study III, which were done in R.

Study I

Exploratory and confirmatory factor analyses (EFA and CFA) were undertaken to examine the factor structure of the CAQ. The sample was randomly divided in two equal splits, where the exploratory analysis was done in one and the confirmatory in the other.

Common factor analysis was used for exploratory purposes in the current study. The Keyser-Meyer-Olkin (KMO) test was used to examine sampling adequacy. Factor analysis was calculated on the basis of a polychoric correlation matrix and then rotated with oblique (promax) rotation. The number of factors to retain was judged based on the Kaiser criterion, visual inspection of Scree plot, Velicer's map criteria, parallel analysis and interpretability and adherence to theory. A salient factor loading was calculated based on sample size. A factor had to contain at least 3 items and any item that had either no salient loading or several salient loadings was removed.

Confirmatory factor analysis was performed using mean-and-variance corrected statistics for Structural Equational Modelling. Model fit was judged based on the values of root mean square error of approximation (RMSEA), comparative fit index (CFI), and Tucker–Lewis index (TLI). Model fit was examined for all factor solutions previously suggested in literature, the solution arrived at in the EFA, and a 1-factor solution.

Tests of validity and reliability was also performed in the same split as the CFA. These tests consisted of examining internal consistency (Cronbach's alpha), test-retest correlations (5 weeks between measurement points), and convergent and discriminant correlations against other anxiety and depression questionnaires. All correlations were performed using Spearman's rho, due to the ordinal level of the data.

Study II

Multiple Cox Regression was performed to calculate the relative risk (Hazard Ratio; HR) of a major cardiovascular event (MACE) under a determined follow-up time. MACE was represented by a composite variable consisting of the following diagnoses: CV death, ACS, heart failure (HF), stroke and coronary revascularisation. The mean follow-up time was 2.92 years and the maximum 5.25 years.

Five different regression models were fitted, where HADS-A, CAQ-T, CAQ-F, CAQ-Av and CAQ-Att served as predictors in each respective model. Additional potentially confounding variables were added, these were: age, sex, education, country of birth, treatment allocation, history of MI, hypertension, diabetes, self-reported social support and depression.

AR was then calculated on the bases of these models at set values of each anxiety scale at -1 SD, mean, +1 SD, and +2 SD.

Study III

Linear Mixed Models were used to estimate the effect of beta-blocker treatment on anxiety and depression at 6-10 weeks and 12-14 months after the MI. This approach accounts for both fixed and random sources of variability and is well-suited for repeated measures data. The model included a fixed effect for follow-up point, beta-blocker randomisation group, and their interaction to assess whether the change in outcome differed between groups. The interaction term allowed us to test whether the effect of the medication varied across the two time points. A random intercept for each participant was included to account for individual differences in baseline symptom levels. This helped handle within-subject correlation due to repeated measures. Additional variables were included to increase statistical power and precision: education, immigration status, age and sex.

The main analysis followed the intention-to-treat principle (ITT), with multiple imputation of missing observations.

Additionally, the main analysis was repeated but in the two separate strata of individuals who already had beta-blocker medication before inclusion, and those who did not have, respectively.

Study IV

Newcastle-Ottawa quality assessment scale (NOS) for cohort studies and an adapted version for cross-sectional studies were used to assess risk of bias. The NOS consists of the three dimensions selection, comparability and outcome, where the selection dimension can be awarded four stars and the comparability dimension two stars for both versions. The outcome dimension can be awarded three stars in the cohort version, and two stars in the cross-sectional version. High risk of bias is typically defined as < 6 stars, medium risk at 6-7 (cohort) and 6 (cross-sectional), and low risk at 8-9 (cohort) and 7-8 (cross-sectional) (Luchini et al., 2017; Ribeiro et al., 2020). Studies were evaluated based on the design according to the research question of this review (MINOCA / TS being exposure and mental health being the outcome). Therefore, a study could have been defined differently by the original authors than what was done in this review.

The results extracted in the review were categorised by the direction of the association (worse, neutral or better) of mental health and QoL, by risk of bias, and by comparison (compared to other groups or change over time).

Study V

Logistic regression was used to estimate the effect of ICBT on a composite outcome of anxiety and stress 10-12 weeks after randomisation. The analysis followed the ITT-principle and missing values were handled with multiple imputation. The primary composite outcome consisted of the proportion of patients in the treatment group compared to the control group that reported below clinical levels of both stress and anxiety, assessed by the cut-off values on PSS-14 (< 25) and HADS-A (< 8). Additional variables were included to increase statistical power and precision: age, sex, and baseline values of the outcomes.

Sensitivity analyses included 1) a per-protocol analysis, 2) an analysis using list-wise deletion instead of multiple imputation, and 3) an outlier analysis. Outliers were identified based on the residuals from the linear regression models of the PSS-14 and HADS-A outcomes, using box plots following Tukeys rule of > 1.5 interquartile range (IQR) (Tukey, 1977). Subsequently logistic and linear regression analyses were then conducted concerning the two primary outcomes, after sequential removal of these outliers.

Secondary consisted of logistic regression estimating the proportion of patients reporting below clinical ratings of either stress or anxiety separately, and linear regression analyses of continuous outcomes PSS-14, HADS-A, HADS-D, CAQ and IES-6. Effect sizes were calculated as Cohen's d, using a pretest-posttest-control group design, following the $_{dppc2}$ formula (S. B. Morris, 2008).

Results

Study I

The study sample consisted of 930 patients for the U-CARE Heart trial that answered the CAQ during screening. The participants had a mean age of 62.2 (SD: 8.1) and 76% (n: 711) were males.

Exploratory Factor Analysis

The KMO value was 0.88 and indicated that the data was adequate for conducting EFA. The Kaiser Eigenvalue criterion, scree plot (see Figure 1), parallel analysis and Velicer's map criteria indicated that 2-8 factor solutions should be rotated. After rotation, based on the criteria for interpretation, a 3-factor, 15-item solution was deemed most reasonable. In this solution items 4, 10 and 13 were removed due to cross-loadings. CAQ-F had two less items and was renamed Fear/Worry (CAQ-FW) due to its emotional and cognitive content, CAQ-Av remained identical to the original version of the CAQ and its name was not changed, and CAQ-Att having one less item (CAQ-Att2). See Table 3 for factor loadings.

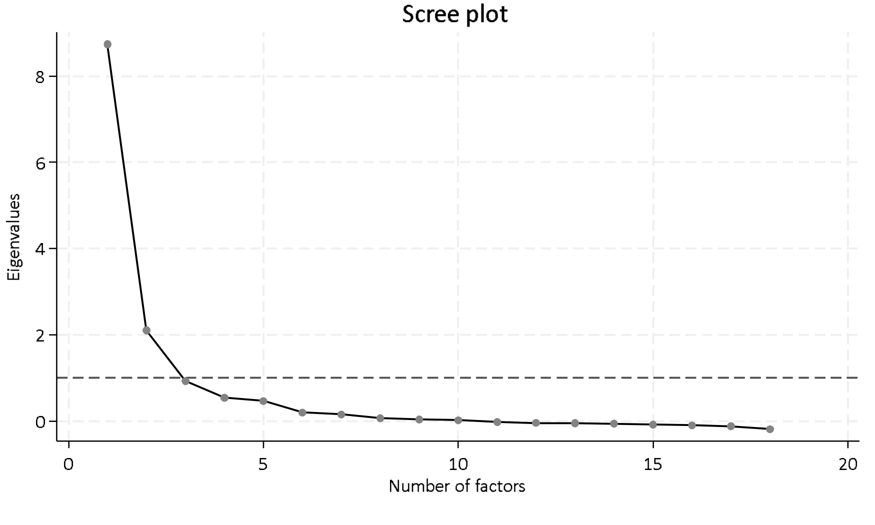

Figure 1. Scree plot of eigenvalues after EFA. Horizontal line is set at eigenvalue = 1.

Table 5
Common Factor Analysis

Item	Fear/ Worry	Avoid-ance	Atten-tion
Fear / Worry			
11. I feel safe being around a hospital, physician, or other medical facility*	**0.56**	0.18	0.10
14. When I have chest discomfort or I feel my heart is beating fast I worry that I may have a heart attack*	**0.84**	0.01	0.09
15. When I have chest discomfort or I feel my heart is beating fast I have difficulty concentrating on anything else*	**0.76**	0.07	0.21
16. When I have chest discomfort or I feel my heart is beating fast I get frightened*	**0.88**	-0.02	0.10
17. When I have chest discomfort or I feel my heart is beating fast I like to be checked out by a doctor*	**0.93**	-0.10	-0.09
18. When I have chest discomfort or I feel my heart is beating fast I tell my family or friends*	**0.61**	-0.02	-0.16
Avoidance			
2. I avoid physical exertion**	0.01	**0.92**	-0.07
5. I take it easy as much as possible**	0.21	**0.53**	-0.03
7. I avoid exercise or other physical work**	-0.13	**0.97**	0.01
9. I avoid activities that make my heart beat faster**	0.09	**0.82**	0.08
12. I avoid activities that make me sweat**	0.00	**0.91**	-0.01
Attention			
1. I pay attention to my heart beat***	0.10	0.01	**0.76**
3. My racing heart wakes me up at night***	0.22	0.05	**0.56**
6. I check my pulse***	0.04	-0.03	**0.54**
8. I can feel my heart in my chest***	0.14	-0.03	**0.70**
Removed			
4. Chest pain/discomfort wakes me up at night***			
10. If tests come out normal, I still worry about my heart*			
13. I worry that doctors do not believe my chest pain/discomfort is real*			

Rotated (promax) EFA. A loading > .24 is displayed in bold. *Part of the factor Fear in the original model. **Part of the factor Avoidance in the original model. ***Part of the factor Attention in the original model

Confirmatory Factor Analysis

Only the factor solution generated by the EFA and a previously suggested 10-item version (Dragioti et al., 2011) demonstrated acceptable model fit in the CFA. Neither the original 18-item version (Eifert et al., 2000), any of the 4-factor solutions (Chiasson et al., 2019; Israel et al., 2017; Marker et al., 2008; Van Beek et al., 2012) nor the 2-factor solution (Sardinha et al., 2013b) demonstrated acceptable model fit (See Table 4 for an overview of model fit statistics).

Table 6

Confirmatory Factor Analysis

Model	Model specification	RMSEA	CFI	TLI
1-factor	1 factor, 18 items	.154	.664	.619
Eifert, 2000	3 factors, 18 items	.086	.898	.882
Marker, 2008	4 factors, 18 items	.083	.906	.889
Dragioti, 2011	3 factors, 10 items	.073	.970	.958
Van Beek, 2012	4 factors, 18 items	.085	.903	.886
Sardinha, 2013	2 factors, 14 items	.097	.911	.893
Israel, 2017	4 factors, 18 items	.084	.906	.888
Generated by EFA	3 factors, 15 items	.075	.938	.925

Table includes: Root mean squared error of approximation (RMSEA), Comparative fit index (CFI), Tucker-Lewis Index (TLI) & Chi2 with n = degrees of freedom (χ^2 (*df*)). ***P < 0.001

Validity and Reliability

The subscales of the 18-item version had α = 0.89 (CAQ-F), α = .87 (CAQ-Av) and α = .70 (CAQ-Att), and the new subscales of the 15-item version had α = .86 (CAQ-FW), and α = .67 (CAQ-Att2).

Test-retest correlations for the 18-item and the 15-item versions were ρ = .75. CAQ-F, CAQ-Av and CAQ-Att in the 18-item version had ρ = .64, .76 and .75 and in the 15-item version ρ = .63, .74, .75, respectively.

Convergent correlations of the original 18-item version with other anxiety questionnaires were slightly higher (HADS-A, ρ = .66; PCL-C, ρ = .70) than with the depression questionnaires (HADS-D, ρ = .60; BADS-SF, ρ = -.56; MADRS-S, ρ = .63).

Study II

The study sample consisted of all 935 patients that participated in the screening of the U-CARE Heart trial. The participants had a mean age of 62.2 (SD: 8.1) and 76% (n: 715) were males.

Association of anxiety with risk of recurrent cardiac events

When adjusting for the predetermined set of covariates, the estimated HR for the composite CV endpoint was 1.52 (95% CI 1.15, 2.02) for HADS-A, and 1.30 (95% CI 1.04, 1.64) for CAQ-T. The strength of evidence for the association between the endpoint event and HADS-A was strong (p=.003) and moderate for CAQ-T (p=0.021). Out of the three CAQ subscales, the estimated HR for the composite CV endpoint was 1.37 (95% CI 1.15, 1.64) for CAQ-Av, and there was strong evidence for this association (p<.001). Insufficient evidence of an association was found for CAQ-F and CAQ-Att (p=.354 and .259) (See Figure 2 and Table 5).

The AR for each anxiety scale and subscale is reported in Table 6. The risk differences between the mean value and +1 SD were 5.7%-points (%-pt.) for HADS-A, 3.3%-pt. for CAQ-T, 1.3%-pt. for CAQ-F, 4.2%-pt. for CAQ-Av, and 1.1%-pt. for CAQ-Att.

Table 7

Cox Regression for Composite Endpoint

	Crude HR (95% CI)	p	Adj. HR (95% CI)	p
HADS-A	1.28 (1.09-1.50)	0.003	1.52 (1.15-2.02)	0.003
CAQ-T	1.35 (1.16-1.61)	0.002	1.30 (1.04-1.64)	0.021
CAQ-F	1.19 (1.01-1.40)	0.037	1.10 (0.90-1.35)	0.354
CAQ-Av	1.51 (1.30-1.75)	< 0.001	1.37 (1.15-1.64)	0.001
CAQ-Att	1.19 (1.01-1.40)	0.033	1.11 (0.92-1.34)	0.259

Each measure of anxiety is adjusted for by age, sex, country of birth, education, social support, depressive symptoms, previous myocardial infarction, infarct type, left ventricular ejection fraction, diabetes, and hypertension. The c-statistic represents each individual model and includes adjusted variables. HADS, Hospital Anxiety and Depression Scale; CAQ, Cardiac Anxiety Questionnaire; HADS-A, anxiety subscale; CAQ-T, total score; CAQ-F, fear subscale; CAQ-Av, avoidance subscale; CAQ-Att, attention subscale

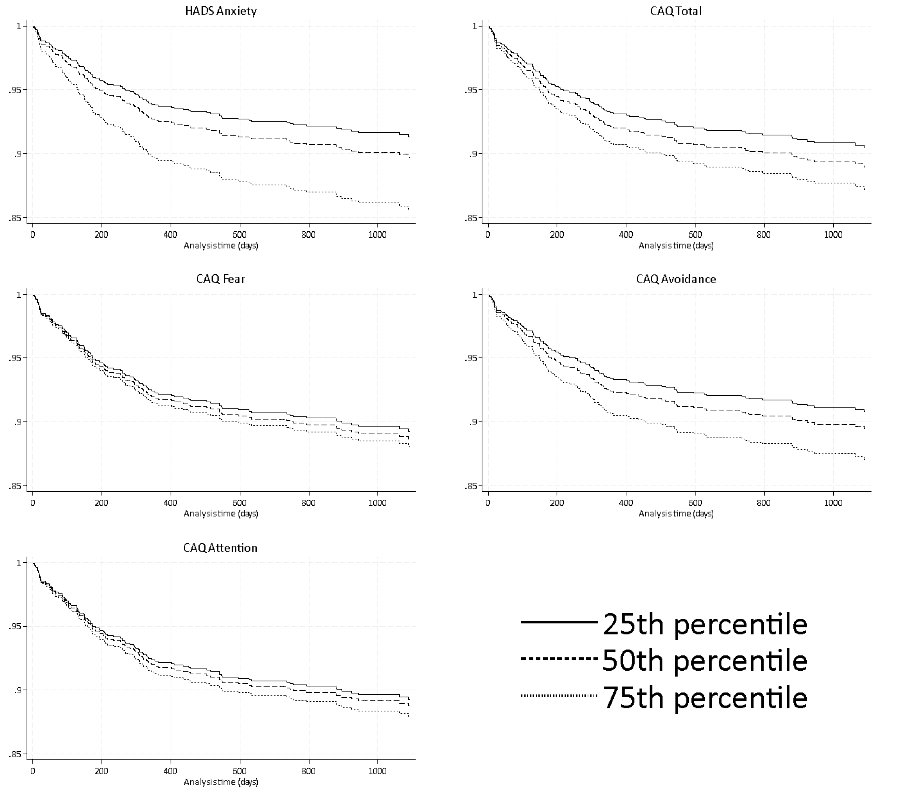

Figure 2. Plot of survival function from main analysis of each anxiety measure. Lines represent survival function at the 25th, 50th, and 75th percentiles of respective anxiety measure.

Sensitivity Analyses

Running the main analysis without multiple imputation yielded essentially identical results. Results of analyses of individual endpoint events showed a variation where HF was related to CAQ-Av but not HADS-A, while the opposite was true for MI-CAD. Excluding the treatment group did not change the support for other associations than HADS-A for which the association with MACE was no longer supported (p=.291).

Table 8
Absolute Risk at 3 years

	-1 SD	Mean	+1 SD	+2 SD
HADS-A	8.8%	12.9%	18.6%	26.3%
CAQ-T	10.0%	12.6%	15.9%	19.8%
CAQ-F	11.8%	12.9%	14.2%	15.5%
CAQ-Av	9.0%	12.2%	16.3%	21.6%
CAQ-Att	11.9%	13.0%	14.1%	15.3%

Absolute risks are predicted from set values on anxiety scales at 3 years follow-up based on Cox models, covariates age, sex, country of birth, education, social support, depressive symptoms, previous myocardial infarction, infarct type, left ventricular ejection fraction, diabetes, and hypertension. HADS, Hospital Anxiety and Depression Scale; CAQ, Cardiac Anxiety Questionnaire; HADS-A, anxiety subscale; CAQ-T, total score; CAQ-F, fear subscale; CAQ-Av, avoidance subscale; CAQ-Att, attention subscale

Study III

The study sample consisted of 806 individuals randomised to beta-blocker or no beta-blocker treatment. The participants had a mean age of 65.7 (SD: 10.4) and 77% (n: 624) were males.

Effects of beta-blockers on anxiety and depression

When running the regression model for the main analysis, the estimated β of the beta-blocker randomisation group at follow-up 1 was 0.48 (95% CI 0.09-0.86), and at follow-up 2 0.41 (95% CI 0.01, 0.81) for HADS-D. There was moderate evidence of this effect at both follow-up 1 (p=.015) and follow-up 2 (0.047). There was insufficient evidence of an effect on HADS-A at both follow-up 1 (p=.777), and follow-up 2 (p=.228). (See Figure 3 and Table 7).

When investigating interactions for both outcomes, no evidence for an interaction between beta-blocker randomisation group and sex was found (HADS-D: p=.837; HADS-A: p=.351), nor between beta-blocker randomisation group and follow-up point (HADS-D: p=.744; HADS-A: p=.114).

Overview of the results from stratified analyses among patients without and with beta-blocker treatment prior to randomisation can be seen in Table 7.

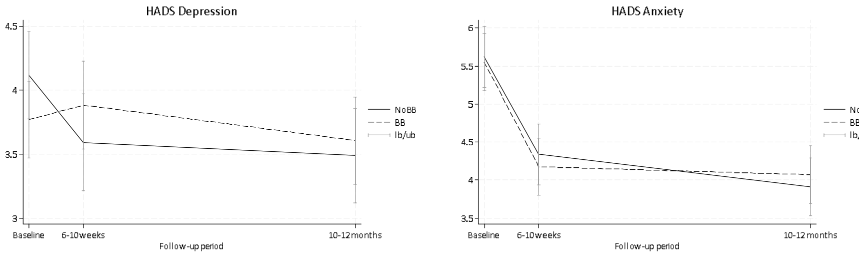

Figure 3. Time-series graph of self-reported anxiety and depression at baseline, follow-up 1 and follow-up 2. Note: values on the y-axis do not reflect the full range of the scales.

Table 9

Regression Coefficients if randomised to beta-blocker treatment

	2 months		12 months		Interaction*
	β (95% CI)	p-value	β (95% CI)	p-value	p-value
Main analysis (N = 806)					
HADS Depression	.48 (.09, .86)	0.015	.41 (.01, .81)	0.047	0.744
HADS Anxiety	-.06 (-.45, .34)	0.777	.26 (-.16, .68)	0.228	0.114
Sub-group, without beta-blocker at baseline (N = 694)					
HADS Depression	.41 (-.00, .82)	0.050	.27 (-.16, .70)	0.222	0.516
HADS Anxiety	-.12 (-.55, .31)	0.584	.27 (-.18, .73)	0.240	0.069
Sub-group, with beta-blocker at baseline (N = 111)					
HADS Depression	.67 (-.41, 1.75)	0.224	1.17 (.03, 2.31)	0.044	0.363
HADS Anxiety	.26 (-.81, 1.33)	0.638	.22 (-.90, 1.34)	0.703	0.942

Adjusted for age, education, if born in Sweden, sex and baseline assessment of outcome. Model includes interaction between variable for follow-up point and randomisation group, as well as between follow-up point and baseline assessment of outcome.

Data on prior registration of beta-blocker medication has 1 missing data point.

***Interaction between variable for follow-up point and randomisation group.**

Sensitivity Analyses

Repeating the analysis, only using complete cases and no multiple imputation led to results very similar to the main analysis (see Table 8).

When repeating the main analysis without adjusting for baseline values of the outcomes the estimated β of the beta-blocker randomisation group at follow-up 1 was .28 (95% CI -.18, .74), and at follow-up 2 was .23 (95% CI -.25, .71) for HADS-D. The evidence of these effects was insufficient (follow-up 1: p=.233; follow-up 2: p=.350). There was still insufficient evidence for any effect on HADS-A at either follow-up 1 (p=.744) or follow-up 2 (p=.353).

Table 10

Sensitivity analysis, without baseline values as covariates

	2 months		12 months		Interaction*
	β (95% CI)	p-value	β (95% CI)	p-value	p-value
HADS Depression	.28 (-.18, .74)	0.233	.23 (-.25, .71)	0.350	0.799
HADS Anxiety	-.08 (-.56, .40)	0.744	.24 (-.26, .74)	0.353	0.114

Adjusted for age, education, if born in Sweden and sex. Model includes interaction between variable for follow-up point and randomisation group.

***Interaction between variable for follow-up point and randomisation group.**

Study IV

Search Results

Nine thousand three hundred and thirty publications were found in the initial search, of which 2,322 were duplicates. Screening for title and lead to a removal of 6,930 publications. Of the remaining publications, 50 were removed during full-text screening, leading to a final amount of 28 studies to be included, meeting the inclusion criteria.

Study characteristics

Sample sizes ranged between 13 to 5,322, with a total of 15,572 participants, including comparison groups. Out of the included participants, 1,241 were MINOCA patients and 898 were TS patients. Looking at studies including MINOCA-patients the mean and median sample size was 1,303 and 473, respectively. The mean and median sample sizes of TS-studies was 262 and 85, respectively.

Quality assessment

The risk of bias assessment in the cross-sectional studies was deemed low in 1 study, medium in 1 study, and high in 16 studies (range: 2–7, average: 4.6). The risk of bias assessment in the cohort studies was deemed low in 2 studies, medium in 6 studies, and high in 2 studies (range: 5–9, average: 6.6). The average rating of studies of MINOCA-patients was 5.9, and the average of studies of TS-patients was 5.1. See Tables 11 and 12 for an overview of study characteristics and their evaluated risk of bias.

Table 11

Study characteristics and risk of bias of studies including MINOCA-patients

Study	RB	n	SD	Comparator	Outcomes
Safdar et al. (2018)	9	2690	C	CHD	Depression, perceived stress
Grodzinsky et al. (2015)	7	5539	C	CHD	Depression, mental QoL
Parvand et al. (2022)	6	154	C	WG	QoL, mental health
Daniel et al. (2018)	5	296	CS	HC, CHD	Anxiety, depression
Daniel et al. (2017)	5	270	CS	HC, CHD, TS	Mental and physical QoL
Izquierdo Coro-nel et al. (2023)	5	533	C	CHD	Anxiety, insomnia
Berg et al. (2023)	5	459	C	TS, HC	Health-related QoL
Hausvater et al. (2023	5	486	C	CHD	Stress, depression

RB: risk of bias, SD: study design, C: cohort, CS: cross-sectional, CHD: coronary heart disease, HC: healthy controls, WG: within-group TS: takotsubo syndrome, QoL: quality of life.

Narrative synthesis

Summary by risk of bias and comparator

In Figures 4-6, results from the different studies are summarised based on risk of bias, comparator, and direction of association with mental health status or QoL.

Among the included studies, there were 19 that compared MINOCA- or TS-patients with cardiac groups.

Here, one study found that that MINOCA-patients reported lower ratings of stress and depression compared with CHD-patients (Hausvater et al., 2023). However, these differences were marginal (stress median scores 7 vs. 6; depression median scores 1 vs. 1), and the risk of bias in this study was evaluated as high.

Nine studies found that MINOCA- or TS-patients reported non-different ratings of mental health and QoL, and among these 7 were evaluated to have a high risk of bias and two a low risk of bias. Out of the two studies with low risk of bias, one followed TS-patients over 15 years and found that while the had a higher risk of rehospitalisation for mood disorders (HR:1.22, 95% CI: 0.72-2.07) and stress and anxiety disorders (HR:1.42, 95% CI: 0.94-2.14), compared with MI-patients, this risk difference was not statistically significant (Auger et al., 2020). The other study with low risk of bias compared TS-patients with MI-patients, 8 weeks after discharge (Wallström et al., 2016). While TS-patients reported higher levels of anxiety (7 vs. 5.7), depression (5.4 vs. 3.9), and stress (23.4 vs. 22.2), neither of these differences achieved statistical significance.

Another 9 studies found that MINOCA- or TS-patients reported worse mental health or QoL, and the risk of bias was here evaluated as low in 2 studies, medium in 2 studies, and high in 5 studies. Out of the two studies with low risk of bias, one of them compared TS-patients with AMI-patients and while they did not find any baseline differences between the two groups regarding anxiety, depression or health-related QoL, at the 1-year follow-up, TS-patients reported significantly worse depressive ratings, as well as worse emotional QoL and self-confidence (Compare et al., 2014). The other low risk of bias study compared TS-patients with ACS-patients with a mean follow-up time of 33.8 ± 21.1 months (Goh et al., 2016). This study found that anxiety was associated with TS (OR: 1.13, 95% CI: 1.01-1.26), but depression was not (OR:0.94, 95% CI: 0.83-1.05).

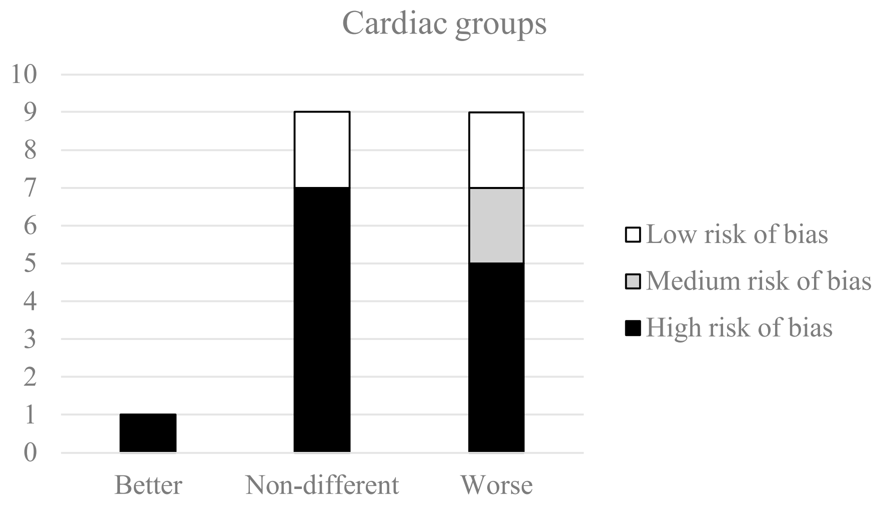

Figure 4. Bar graph of number of studies by risk of bias, categorised by direction of association between MINOCA-/TS-diagnosis and mental health status or QoL, compared with cardiac groups.

Among the included studies, there were 12 that compared MINOCA- or TS-patients with non-cardiac groups.

While there were no studies here that found healthy controls to have better mental health or QoL compared to MINOCA- or TS-patients, there were three studies that found non-different results. These studies were all evaluated at high risk of bias.

Out of the nine studies that found MINOCA- or TS-patients to have worse mental health or QoL one of them was evaluated at low risk of bias and the remaining 8 at high risk of bias. The low risk of bias study was the same study that was previously described, following TS-patients over 15 years and did not find a statistically significant difference in risk compared with MI-patients (Auger et al., 2020). However, in comparison with populations controls, TS-patients had a higher risk of rehospitalisation for stress and anxiety disorders (HR: 1.86, 95% CI: 1.12-2.85) that was statistically significant. The risk for rehospitalisation regarding mood disorders was similar as when compared with MI-patients (HR: 1.34, 95% CI: 0.78-2.29).

Table 12
Study characteristics and risk of bias of studies including TS-patients

Study	RB	n	SD	Comparator	Outcomes
Auger et al. (2019)	9	3650	C	CHD, HC	Mood disorder, stress and anxiety disorder
Wallström et al. (2016)	7	127	CS	CHD	Anxiety, depression, stress, sleep disturbance
Compare et al. (2014)	7	74	C	CHD	Anxiety, depression, QoL, Psychological distress
Goh et al. (2016)	6	184	CS	CHD	Anxiety, Depression
Saffari et al. (2017)	6	188	C	CHD	Sexual functioning, anxiety, depression
Sundelin et al. (2020)	6	20	C	WG	Stress
Waldenbourg et al. (2011)	6	13	C	WG	Post-traumatic stress, depression
Christensen et al. (2016)	5	173	CS	HC, CHD	Well-being, anxiety, depression
Compare et al. (2018)	5	111	CS	HC, TS-nt	Depression
Delmas et al. (2013)	5	95	CS	CHD	Psychiatric disorders
Naegele et al. (2016)	5	43	CS	MC	QoL
Salmoraigo-Blotcher et al. (2016)	5	107	CS	HC, CHD	Psychological distress, stress, post-traumatic stress
Gorini et al. (2022)	4	40	CS	CHD	Anxiety, post-traumatic stress
Kastaun et al. (2014)	4	59	CS	HC. CHD	Psychiatric symptoms, depression, stress
Olliges et al. (2020)	4	136	CS	HC, CHD	Anxiety, depression, QoL
Sancassiani et al. (2018)	4	95	CS	HC	QoL, anxiety disorders, post-traumatic stress disorder
Smeijers et al. (2016)	4	56	CS	HC, HF	Anxiety, depression, stress
Zarifeh et al. (2012)	4	17	CS	NCCP, CHD	Anxiety, depression, post-traumatic stress
Lazzeroni et al. (2022)	3	19	CS	HC	Anxiety, depression
Sabisz et al. (2016	2	26	CS	Norms	Anxiety, depression

RB: risk of bias, SD: study design, C: cohort, CS: cross-sectional, CHD: coronary heart disease, HC: healthy controls, WG: within-group MC: matched controls TS: takotsubo syndrome, TS-nt: takotsubo syndrome no emotional trigger, NCCP: non-cardiac chest-pain, QoL: quality of life

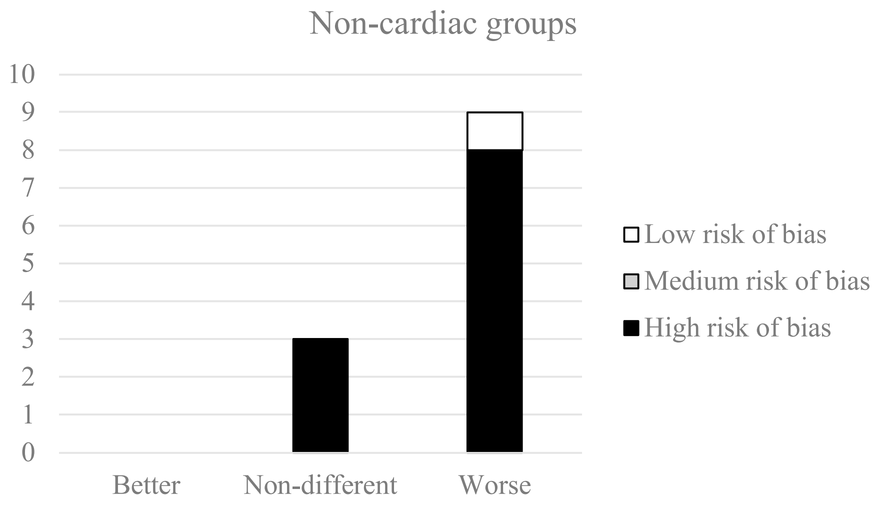

Figure 5. Bar graph of number of studies by risk of bias, categorised by direction of association between MINOCA-/TS-diagnosis and mental health status or QoL, compared with non-cardiac groups.

Among the included studies, there were 5 that investigated change over time for MINOCA- and TS-patients.

Three out of these studies reported that MINOCA- or TS-patients report improving mental health or QoL symptoms over time. One of these studies was evaluated as high risk of bias and the other two as medium risk of bias. Out of the two studies at medium risk of bias, one followed TS-patients and found that average stress ratings decreased from baseline (median 30.5) to the 1-year follow-up (median 20.5), and this difference was statistically significant (Sundelin et al., 2020). Still, around 1/3 of the TS-patients reported elevated stress ratings at the 1-year follow-up (> 25 on the perceived stress scale). The other study found that, for MINOCA-patients, while self-reported QoL had improved at the 1-year follow-up, ratings of depression remained unchanged (Parvand et al., 2022).

One of these studies, evaluated at medium risk of bias, did not find any statistically significant differences in TS-patients for ratings of depression or post-traumatic stress at the 3-month follow-up (Waldenborg et al., 2011).

One of these studies, also at a medium risk of bias, found that TS-patients reported worse depressive ratings and health-related QoL at the 1-year follow-up, compared with baseline (Compare et al., 2014).

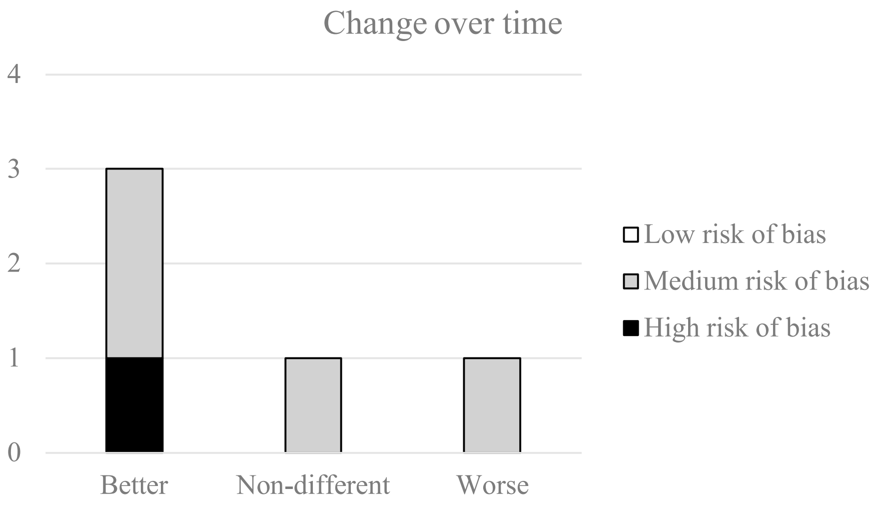

Figure 6. Bar graph of number of studies by risk of bias, categorised by direction of association between MINOCA-/TS-diagnosis and mental health status or QoL over time.

Comparison of MINOCA and TS

Two studies compared MINOCA- and TS-patients with each other. Both of these studies were evaluated at a high risk of bias and used the SF-36 outcome measure to assess various aspects of QoL. One of them found that TS-patients had worse emotional well-being 3 months after the event (60 vs. 76, p=0.001), compared to MINOCA-patients (Daniel et al., 2017). The other study found that TS-patients reported worse emotional well-being during hospitalisation (58.4 vs. 69.7, p=0.004) but not 1 year after the event (70.1 vs 77.4, p=0.101)

Findings regarding symptoms of anxiety

Studies investigating anxiety as an outcome after MINOCA or TS are reported in Table 13. Nine of 15 studies (60%) found anxiety to be worse in MINOCA- or TS-patients compared either to cardiac nor non-cardiac groups. Five of these were compared to cardiac groups, and four were compared to non-cardiac groups. The other 6 out of 15 studies (40%) reported no difference in anxiety, either compared to cardiac groups (4 studies), or to non-cardiac groups (1 study). There was also one additional study that reported anxiety symptoms over time and found that they were unchanged one year after the event (Compare et al., 2014).

Table 13

Study characteristics and risk of bias of studies assessing anxiety

Study	Comparison	Outcome
Auger et al. (2019)	TS vs. HC	HR: 1.86, 95% CI: 1.12-2.85
	TS vs. CHD	HR: 1.42, 95% CI: 0.94-2.14
Wallström et al. (2016)	TS vs. CHD	7.0 vs. 5.7, p=0.721
Compare et al. (2014)	TS vs. CHD	77.4 vs. 77.8, p>0.05
	TS, acute vs 12 month	77.4 vs. 78.1, p>0.05
Goh et al. (2016)	TS vs. CHD	OR: 1.13 (1.01-1.26)
Daniel et al. (2018)	MINOCA vs. HC	5.5 vs. 3.3, p<0.001
	MINOCA vs. CHD	5.5 vs. 4.2, p=0.049
Christensen et al. (2016)	TS vs. HC	2.0 vs. 1.0, p=0.007
	TS vs. CHD	2.0 vs. 1.0, p<0.001
Izquierdo Coronel et al. (2023)	MINOCA vs. CHD	19.0 vs. 19.0, p=0.6
Smeijers et al. (2016)	TS vs. HC	2.1 vs. 1.3, p=0.039
		3.3 vs. 1.9, p=0.170
	TS vs. HF	2.1 vs. 2.6, p=0.561
		3.3 vs. 3.8, p=0.940
Zarifeh et al. (2012)	TS vs. NCCP	5.3 vs. 8.2, p>0.05
	TS vs. CHD	5.3 vs. 6.6, p>0.05
Lazzeroni et al. (2022)	TS vs. HC	2.7 vs. 0.8, p=0.121
Sabisz et al. (2016	TS vs. norms	54% above norm
Olliges et al. (2020)	TS vs. norms	1.94 vs. 0.94
	TS vs. CHD	1.94 vs. 1.56, p=0.06
Sancassiani et al. (2018)	TS vs. HC	OR: 1.35, 95% CI: 0.05-16.19
		OR: 5.95, 95% CI: 1.52-23.19

TS: takotsubo syndrome, HC: healthy controls, CHD: coronary heartdisease, MINOCA: myocardial infarction without obstructive coronary arteries, HF: heart failure, NCCP: non-cardiac chest pain.

Outcomes are reported as either relative risk (OR, HR) with 95% CI, or numerical values of groups with a p-value (if available) indicating a statistical test of difference. For the specific outcome measures used in each study, I refer to the main manuscript (Leissner, Olsson, et al., 2025)

The majority (6/9) of studies finding that MINOCA- or TS-patients report worse levels of anxiety were assessed at follow-ups later than 3 months after the event (Auger et al., 2020; Christensen et al., 2016; Goh et al., 2016; Olliges et al., 2020; Sabisz et al., 2016; Smeijers et al., 2016). Two of the studies were in the acute phase (Delmas et al., 2013; Saffari et al., 2017), and one study in the interval after discharge, up until 3 months (Daniel et al., 2018).

Regarding the studies that found no difference in anxiety symptoms, two were in the acute phase (Compare et al., 2014; Coronel et al., 2023), and four were in the interval between discharge up until three months after the event (Lazzeroni et al., 2022; Sancassiani et al., 2018; Wallström et al., 2016; Zarifeh et al., 2012).

Three of the studies investigating differences in anxiety were evaluated as low risk of bias (Auger et al., 2020; Compare et al., 2014; Wallström et al., 2016). Neither of these studies found differences that were statistically significant, although one reported a numerically higher risk of rehospitalisation for stress and anxiety (Auger et al., 2020), and another numerically higher levels of anxiety (Wallström et al., 2016), as reported above.

Study V

The study sample consisted of 88 individuals that were randomised to ICBT or a waiting list. The mean age of the participants was 62.9 (SD: 9.9) and 9% (n: 8) were males.

Treatment effect on binary outcomes

When running the primary, pre-specified, analysis of the composite outcome, the estimated OR was 2.37 (95% CI: .88 – 6.38), and the evidence for this effect was weak (p-value: 0.088). When analysing the two primary outcomes separately the estimated OR for PSS-14 was 2.18 (95% CI: .81 – 5.85) and for HADS-A 2.75 (95% CI: 1.01 – 7.51). There was very weak evidence for the effect on PSS-14 (p-value: 0.123), and moderate evidence of an effect on HADS-A (p-value: 0.049). The proportion of patients that reported below clinical levels on the three outcomes can be seen in Figure 6.

Treatment effect on continuous outcomes

In secondary analyses of continuous outcomes, there was a positive estimated treatment effect for every outcome, with very strong evidence for the effect on HADS-A, CAQ-T and CAQ-F (see Table 9 for an overview on all outcomes).

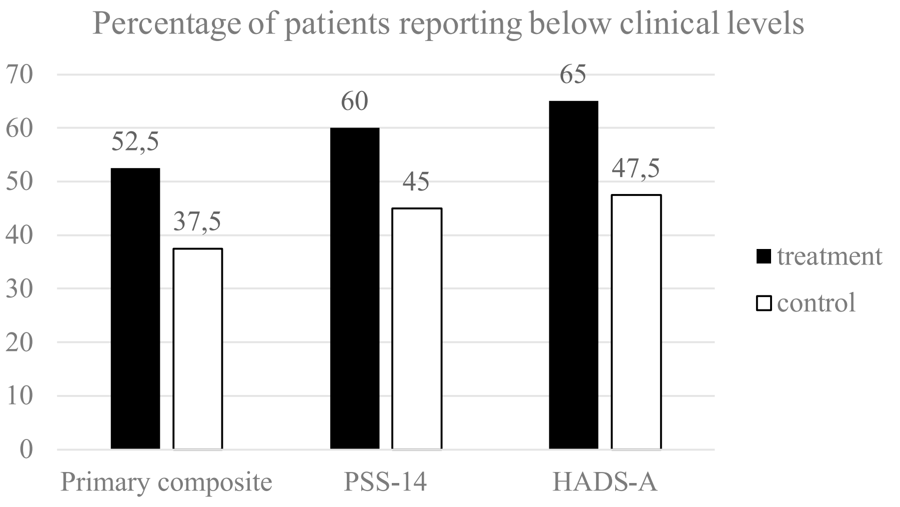

Figure 7. Percentage of patients reporting below clinical levels at the 10–12-week follow-up. Primary composite: below cut-off on both PSS-14 and HADS-A; PSS-14: <25; HADS-A: <8.

Table 13
Continuous outcome variables

	β	95% CI	p-value	Cohen's d
HADS-D	-1.24	-2.52 – .09	0.057	0.37
HADS-A	-1.98	-3.46 – -.50	0.009	0.67
PSS-14	-3.05	-5.90 – -.20	0.036	0.48
Coping	-1.35	-3.10 – .41	0.130	0.30
Distress	-1.76	-3.32 – -.20	0.028	0.53
CAQ	-.27	-.46 – -.07	0.008	0.44
Fear	-.41	-.64 – -.19	< 0.001	0.50
Avoidance	-.23	-.59 – .13	0.201	0.25
Attention	-.18	-.41 – .05	0.120	0.24
IES-6	-2.24	-4.03 – -.45	0.015	0.56

In the linear regressions, pre-randomisation values, age and sex were added as covariates.

Sub-group analyses

Post-hoc analyses revealed strong evidence of interaction effects for the composite primary outcome (p=0.016), and moderately strong evidence for the two primary outcomes separately (PSS-14, p=0.024; HADS-A, p=0.045). Comparatively, the estimated OR for the main composite outcome in the TS-group was 7.41 (95% CI 1.80, 30.53), and in the non-TS group 0.45 (95% 0.08, 2.41). Standardised estimates by diagnosis (TS or non-TS) for the continuous outcomes are visualised as a forest plot in Figure 7.

Sensitivity analyses

When running the per-protocol analysis, excluding those who were randomised to treatment but did not complete the required amount of >4 steps, the estimated OR for the main composite outcome was 2.46 (95% CI: .88, 6.86) and the evidence for this effect was weak (p=0.086).

The estimated OR for the main composite outcome in the non-imputed analysis was 2.17 (95% CI: .80, 5.97) and there was no evidence for this effect (p=0.130).

Additionally, 2 outliers were identified, and repeating the main analysis after excluding these resulted in an OR of 3.55 (95 % CI: 1.18, 10.69) and there was strong evidence for this effect (p=0.024).

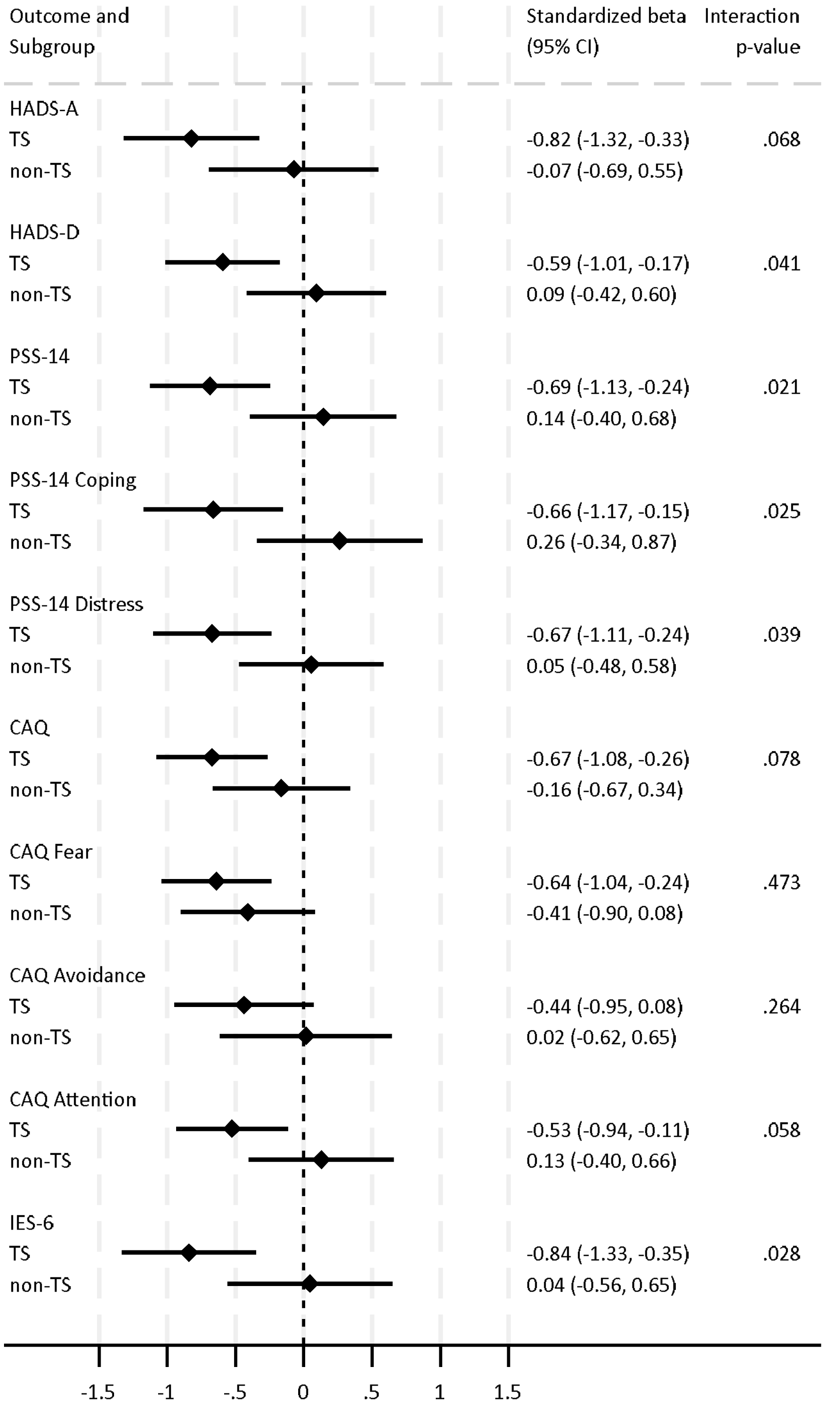

Figure 8. Forest plot of continuous outcomes, subgroups by diagnosis (TS, non-TS). TS: Takotsubo Syndrome, HADS-A: Hospital Anxiety and Depression Scale (anxiety subscale), PSS-14: Perceived Stress Scale (14 items), CAQ: Cardiac Anxiety Questionnaire, IES-6: Impact of Event Scale (6 items).

Discussion

Main findings

In Study I, it was found that the Swedish translation of CAQ showed acceptable psychometric properties in a post-MI sample and that a 3-factor structure similar to the one proposed by the original authors had the best fit to the data.

In Study II, it was found that anxiety proved to be independently associated with the risk of recurrent MACE in post-MI patients, and the specific aspects of anxiety avoidance and arousal were associated with increased risk.

In Study III, it was found that beta-blockers administered to MI-patients with preserved LVEF led to slight increases of depressive symptoms but not symptoms of anxiety. Additionally, the effect on depressive symptoms was particularly pronounced in the sub-group of patients that were randomised to continued use, rather than first-time users.

In Study IV, it was found that in the current literature describing the mental health and QoL of MINOCA and TS patients after their cardiac event, a majority of the studies demonstrate a high risk of bias. However, among the identified studies there was a trend indicating that MINOCA- and TS-patients had equal to or worse mental health than other cardiac groups and that they do no always naturally improve after the event.

In Study V, it was found that ICBT could effectively reduce symptoms of anxiety, stress and post-traumatic stress in MINOCA- and TS-patients, but there was not sufficient evidence to support that it could eliminate clinical levels of both stress and anxiety. Furthermore, sub-group analyses indicated that the treatment was highly effective for TS-patients but not effective for MINOCA-patients.

Validity and reliability of assessing cardiac anxiety

The CAQ has been evaluated in different populations and languages, but given the varying results, the evidence base for its reliability and validity was still uncertain. As such, Study I aimed to use CTT to evaluate these qualities.

The overall findings of the study, based on the EFA and CFA together, suggest that the data is best described by a model with 3 factors, but that some items from the CAQ-F and CAQ-Att have poor fit. CAQ-Av demonstrated no problems in the various tests performed. An interesting finding was that also a 10-item version demonstrated good fit to the data, suggesting that it may be a good suggestion for a short-form (Dragioti et al., 2011).

The removal of three items (4, 10 and 13) was due to cross-loadings between the factors CAQ-FW and CAQ-Att. A fourth item, item 18, also cross-loaded in the first rotation, but did not remain after sequential removal of items and repeated rotation of the factor matrix. While these findings are by no means conclusive, they raise the question regarding the validity of the Swedish 18-item version of the CAQ. It is possible that the high cross-loadings may be due to the items not being specific enough, or that they rather belong to another aspect of anxiety.

Beginning with item 4, “Chest pain/discomfort wakes me up at night”, it is proposed to belong to CAQ-Att, but is arguably rather describing a sense of being startled. This is similar to item 3, “My racing heart wakes my up at night”, which seems to describe a similar experience, reflecting being woken up at night by a reaction to heart-related symptoms. In previous publications, results regarding these two items are inconsistent, as they shift between different subscales, grouped by themselves as “abnormal symptoms (Inyoo et al., 2022), both kept in CAQ-Att (Chiasson et al., 2019; Israel et al., 2017), both included in the new factor “Fear and Hypervigilance” (Sardinha et al., 2013a), putting both items in a subscale named “Worry” (Marker et al., 2008a), and having item 4 loading on CAQ-F (Van Beek et al., 2012). The theoretical justification for having these items in a factor assessing attention is currently unclear, and while they may represent some other factor of CA, two items are too few to create a stable subscale (Watkins, 2018). Future research may be needed to determine the role of sleep disturbances caused by cardiac stimuli.

Item 10, “If tests come out normal, I still worry about my heart”, was removed from the questionnaire in two of the previous publications (Chiasson et al., 2019; Dragioti et al., 2011). The item partially reflects heart-related worry, but also describes a scepticism towards medical tests. It is possible that this item not entirely describes what is known as fear or worry, but perhaps better reflects a subscale in the first CAQ version described as “cardiac disease conviction” (Eifert et al., 1992).

Item 13 “I worry that doctors do not believe my chest pain/discomfort is real” was also removed in the same two studies as Item 10 (Chiasson et al., 2019; Dragioti et al., 2011). Although this item asks the respondents regarding worry, the worry is not referring to the heart itself but to not being believed by doctors. This item might also be an indicator of “cardiac disease conviction”, or rather reflect a general mistrust towards doctors or others in general.

The test-retest correlations indicated that the scale was relatively stable over time, as correlations are expected to decrease with longer follow-up periods (DeVellis, 2006). The scale additionally demonstrated strong correlations with other scales of anxiety (HADS-A, $\rho = .66$; PCL-C, $\rho = .70$), and almost as strongly with scales of depressive symptoms (HADS-D, $\rho = .60$; BADS, $\rho = -.56$; MADRS-S, $\rho = .63$). This could be a reflection that the scale captures the shared aspect of negative affectivity, as posited by the tripartite model of anxiety and depression (Clark & Watson, 1991), and that it is slightly more related to symptom of anxious arousal and PTTS, specifically pertaining to the cardiac event.

Similar to one of the previous studies, we proposed renaming the factor Fear to Fear/Worry. This was based on the fact that many of the items reflect the cognitive aspect worrying and it may be a more accurate label. While, by certain standards, the term fear may to refer to the cognitive appraisal of future threat (Beck et al., 2005), the contemporary definition of anxiety according to APA differentiates anxiety from fear, as "fear is an appropriate, present-oriented, and short-lived response to a clearly identifiable and specific threat" (American Psychological Association, 2025b).

Finally, several previous studies have suggested adding a fourth factor, Reassurance Seeking (Chiasson et al., 2019; Israel et al., 2017; Marker et al., 2008; Van Beek et al., 2012). While this is a theoretically sound suggestion, with reassurance seeking behaviours showing a central role in anxiety disorders (Beesdo-Baum et al., 2012), and being assessed in several other anxiety questionnaires (Rector et al., 2011), these models did not fit the data very well. A possible explanation may be related to the low difficulty level of item 11 "I feel safe being around a hospital, physician, or other medical facility", as it may not function properly in discriminating between high or low anxiety individuals.

In summary, although some limitations with the current version of the CAQ was observed, it seems a reasonably valid and reliable instrument to capture heart-related anxiety. However, future studies might investigate how to improve its reliability, through increased specificity and perhaps reconsidering some parts of its construct validity.

Anxiety as a predictor of recurrent cardiac events

That anxiety is a predictor for increased risk of recurrent MACE is something that has been shown in previous research (Celano et al., 2015; Roest et al., 2010; Wen et al., 2021). The findings of Study II, that anxiety was associated with an increased risk of recurrent MACE, were therefore not that surprising. However, given the somewhat unclear status of psychosocial factors as risk modifiers (Visseren et al., 2021), replication of findings is necessary. Furthermore, by investigating the association of separate symptom clusters with risk of recurrent MACE, further light is shed upon the potential mechanisms of the relationship.

That HADS-A showed the highest risk association with recurrent MACE is in line with the hypothesis of physiological mechanisms mediating the relationship. Comparing these results to previous studies using the HADS as a predictor, one found similar results, with strong evidence of an association between HADS-A and readmission for chest pain or potential IHD (Iles-Smith et al., 2015). It should be noted that readmission differs from cardiac events as endpoints, as it may not be an exact indicator of cardiac health, and could also be driven by the anxious behaviour of reassurance seeking, in otherwise healthy individuals. However, the composite MACE outcome used in Study II included revascularisation which is also not be a certain indicator of worsened cardiac health. And while HADS-A had an association with revascularization individually, evidence linking anxiety to more certain cardiac markers was also found, as there was an association with ACS as well. Somewhat dissimilar from these findings, another study found that when adjusting for disease markers, physical activity, and depression, HADS-A was not associated with the risk of new cardiovascular events (Larsen et al., 2014). That regression model was different compared to the one used in Study II, where physical activity was not adjusted for, as it was theorised to be a mediating rather than a confounding variable. However, the opposite relationship may be possible, and it is difficult to determine without longitudinal data. Still, an important and interesting finding of Study II was that the risk association for HADS-A increased substantially in the adjusted compared to crude analysis (crude HR: 1.28, adjusted HR: 1.52). The adjusted model included symptoms of depression which indicates that anxiety symptoms are a better predictive factor for recurrent MACE. Another study used the Beck Anxiety Inventory (BAI) and found evidence of an increased risk of in-hospital complications among anxious patients (Huffman et al., 2008). The BAI is also considered to assess somatic symptoms of anxiety, and in this study, they adjusted for several disease markers, socioeconomic factors and depression. It should be noted that, although in-hospital complications are prognostically related to readmissions (M. S. Morris et al., 2014), they are a different outcome. Thus, the mechanism of association with increased risk for physiological symptoms of anxiety may differ, although they are likely related.

The second strongest association with risk for recurrent MACE was for CAQ-Av. This finding regarding avoidance has been previously demonstrated in a study of the CAQ (Van Beek et al., 2016), but with a smaller sample size and fewer covariates. While the role of anxious avoidance behaviours is still relatively unexplored when predicting prognosis and CV health, this illustrates it may be an important prognostic marker and target for intervention. A previous study also found that fear of movement (kinesiophobia), was related to several factors potentially influencing rehabilitation and prognosis (Bäck et al., 2013).

On the other hand, neither CAQ-F nor CAQ-Att demonstrated any convincing evidence of risk association with recurrent MACE. These findings are in line with previous research regarding the association of cognitive aspects of anxiety and depression with CVD risk (Schiffer et al., 2009; Van Beek et al., 2016). Some previous studies have even suggested that the cognitive aspects of anxiety may be protective against CVD, by increasing positive health behaviours and more frequent medical visits (Hohls et al., 2020; G. Parker et al., 2011; G. B. Parker et al., 2010), and while it is an interesting and plausible hypothesis there is still very little evidence to support it. Furthermore, a possible explanation for the lacking evidence of association could be attributed to problems of reliability of these subscales, as indicated by the results of Study I.

An important measure of Study II was to illustrate any clinical significance of the findings. It is often recommended to report effect sizes and confidence intervals (Blume & Peipert, 2003), but also to complement estimates of relative risk with absolute risk (Noordzij et al., 2017). As we calculated the absolute risk of each anxiety scale, the largest differences between different anxiety levels could be seen for HADS-A and CAQ-Av. As an example, an individual with -1 SD on the HADS-A had an estimated 8.8% risk of recurrent MACE, while an individual with +2 SD had an estimated 26.3% risk. In this sample the mean (*SD*) of HADS-A was 5 (*4.2*), suggesting the risk for recurrent MACE of an individual with a score of ~1 point on the scale would be 8.8%, while the risk for an individual with a score of ~13 points would be 26.3%. For reference, 13 points on the HADS-A scale indicates clinical levels of anxiety but is below the threshold for severe anxiety which is >15 (Snaith, 2003).

Effects of beta-blockers on anxiety and depression

It is commonly reported that anxiety symptoms are elevated after a cardiac event (Celano et al., 2016; Lian et al., 2021). This may be related to the stressful and life-threatening experience of the event, but also with the associated treatments. In Study III, the potential effect of beta-blockers was considered for both anxiety and depression. As characterised by the tripartite model of anxiety and depression, both symptom clusters may be considered as part of a state of negative affectivity, and separated by anhedonia and physiological arousal (Clark & Watson, 1991). While the HADS-D primarily focuses on symptoms of anhedonia (Langvik et al., 2016), this may also be a consequence of prior symptoms of anxiety (Winer et al., 2017). It is therefore possible that the observed symptoms of anhedonic depression observed in this study, are a consequence of an individual coping with anxiety through avoidance.

Furthermore, while symptoms of depression were marginally higher for patients randomised to beta-blockers, there was no difference observed for anxiety symptoms. The hypothesis was that beta-blockers could have time-varying effects on anxiety, depending on various mechanisms. The immediate effect of beta-blockers could be anxiety relieving, but in the long-term patients could react negatively through reduced inhibitory learning and through unwanted side effects, e.g., insomnia or sexual dysfunction. Notably, a secondary publication from the RQoL trial also found no overall effect of beta-blockers on CA (Leissner, Mars, et al., 2025). However, stratified analyses revealed a potential anxiolytic effect in patients with moderate anxiety, but not in those with low symptom levels. This suggests that beta-blockers may be beneficial for individuals with clinically significant anxiety, an effect confounded by the low average anxiety in the study sample.

There was moderately strong evidence for the effect observed on depressive symptoms. However, a point estimate difference of 0.4-0.5 on the HADS-D is arguably not clinically relevant, as the minimal clinically relevant difference has been suggested to lie in the range of 0.5 and 5.57 points for patients with CVD (Lemay et al., 2019). Furthermore, as previously alluded to, most of these patients would not be considered either clinically anxious or depressed (Bjelland et al., 2002), with symptom levels within the span considered as "normal" (0-7). Still, knowledge of this effect may still be important as even a slight increase of symptoms may trigger or exacerbate an already existing mood disorder. It is also possible that certain individuals or subgroups are more susceptible to the adverse effects of beta-blockers, as indicated by the stratified analysis.

Mental health after MINOCA or TS

In Study IV, we reviewed the evidence of mental health outcomes in patients with MINOCA or TS after the acute event. The finding that these patients demonstrate worse mental health or QoL compared to non-cardiac groups was not unexpected given what we already know about the mind-heart connection (Levine et al., 2021). The more interesting questions were whether these patients also had worse mental health and QoL than other cardiac patients and whether they showed any spontaneous improvement. Unfortunately, it was found that the majority of studies demonstrated a high risk of bias, making any definite conclusions difficult to draw. However, the trend in available data suggests that MINOCA- or TS-patients either have as bad mental health status or QoL as other cardiac groups, or worse. This also seemed to be the case when only looking at the studies with low risk of bias. Additionally, among the studies included in Study IV, while three studies indicated an improvement over time, one study found no change over time and another even reported worsening mental health status over time. This finding suggests that in some cases, patients cannot cope with mental distress symptoms on their own and may be in need of from psychological interventions.

Specifically, 15 studies investigated symptoms of anxiety after the acute event. Findings here were similar to the results regarding mental health in general, they either indicated that levels of anxiety were higher or that there was no difference for MINOCA- and TS-patients compared to other groups. While no strong conclusions can be drawn by counting the number of studies, some interesting observations can be made. For example, among the studies that found higher levels of anxiety in MINOCA- and TS-patients they were most often assessing follow-ups longer than 3 months after the event (6/9 studies), whereas the non-different studies only assessed anxiety in the period between discharge up until 3 months (6 studies). It is possible that this is related to the finding of spontaneously recovering anxiety observed in cardiac patients (Murphy et al., 2020). It is possible that the non-different results are due to this natural elevation of anxiety after the cardiac event, but that MINOCA- and TS-patients experience persistent problems, that doesn't naturally ameliorate.

Few studies compared MINOCA- and TS-patients with each other. However, when they did, the trend was towards TS-patients suffering worse mental health and QoL. Given the interesting sub-group findings of Study V, further research investigating these differences are needed. Looking at the characteristics of the studies investigating either MINOCA or TS, the MINOCA studies were fewer (n: 8), but had a higher average quality assessment (NOS: 5.9) and larger sample sizes (mean: 1,303; median: 473) than TS studies (n: 20; NOS: 5.1; mean: 262; median: 85). This reflects the higher prevalence of MINOCA in the average population, but also highlights the need of methodologically sound study designs investigating TS-patients, to facilitate pooling of results.

Treatment of stress and anxiety after MINOCA or TS

The results of Study IV showed that patients after a MINOCA or TS experience elevated levels of stress and anxiety which may not naturally improve over time. This is a further indication of the potential benefits of the ICBT investigated in Study V.

That psychological interventions are effective for reducing symptoms of anxiety, as well as related symptoms such as stress and depression, in patients with CVD is well known (Ski et al., 2024). As such, the results of Study V were not all that surprising. The evidence for a treatment effect was strong for several of the outcomes, and effect sizes ranged from small to moderate in size. However, evidence for effect on the primary outcome was not very strong. This outcome was defined as the proportion of patients with subclinical ratings on both the PSS-14 and HADS-A in the treatment group. A reason why this discrepancy was observed will be discussed in the methodological section below.

Out of all the outcomes the effect on HADS-A demonstrated the largest effect size. This is an interesting finding, given that only half of the patients in the treatment group did not complete the optional steps on exposure, which was the step of the treatment that was most anxiety-specific. However, as discussed previously, the HADS-A captures physiological symptoms of anxiety, not behavioural. While exposure therapy can reduce arousal for the exposed stimuli, interventions focusing on relaxation and recovery are arguably even more effective for this purpose. Compare instead with the behavioural aspect, assessed with CAQ-Av, where no evidence of an effect was found. Furthermore, the arousal symptoms of anxiety are very similar to the physiological symptoms associated with stress, which was the other main target of the treatment. This indicates that the treatment had the intended effect of reducing symptoms of physiological arousal. The effect on symptoms of posttraumatic stress (PTSS) is also in line with these findings, as physiological arousal is one of the symptom clusters defining PTSD. The effect on PTSS could also be explained by the fact that the repeated recounting of the cardiac event and associated emotions and cognitions share similarities written exposure therapy (DeJesus et al., 2024).

There was also an interesting sub-group effect observed in Study V. Patients with TS appeared to derive substantially more value from the intervention compared to patients with MINOCA. This is indeed an interesting finding, but given that this analysis was not pre-specified, the evidence for these results should be judged accordingly. Still, the differences observed were larger than what would be expected from chance. Future studies are needed to determine whether these results represent a real difference between MINOCA and TS patients, and what the cause is of this potential difference. For example, as some of the MINOCA patients are diagnosed with MI, in Sweden they get access to cardiac rehab, which is associated with better mental health status (Ku et al., 2002; Ruano-Ravina et al., 2016), and may explain why they improve without the need for a psychological intervention. On the other hand, studies tend to report that TS patients have a higher prevalence of psychiatric disorders (Commeau et al., 2022), and they have reported having reduced emotional regulation (C. Klein et al., 2020), which may be an indication that these patients are a more appropriate target for psychotherapy. MINOCA-patient may be more similar to typical MI-CAD-patients, where many improve naturally, while TS-patients may not. More evidence is needed before making any final statement regarding this question, but these intriguing results might be an indication that patients with TS have a pronounced need for psychological interventions.

Considering the risk of recurrent events for MINOCA- and TS-patients, it is possible that the ICBT intervention will lead to improved prognosis for these patients. It has previously been shown for patients after a CHD event, that CBT treating symptoms of stress was associated with a significantly lower risk of recurrent MACE (Gulliksson et al., 2011). In Study II, the aspect of physiological arousal was also associated with a significant risk of recurrent MACE for CHD-patients, which arguably has indiscernible qualities to self-reported stress. While Study V was concerned with treating patients without CHD, psychological interventions may arguably be even stronger in preventing recurrent events for these patients, given their lower prevalence of traditional risk factors. Relating to the sub-group findings, TS-patients have been specifically called out as an important target for psychological interventions (Lisci et al., 2025). As such, given that the ICBT treatment in Study V was especially effective in reducing symptoms of self-reported arousal, as well as self-perceived distress and post-traumatic stress, it might also have promising prognostic effects for the patients' cardiac health.

There is also a potential that there was an interplay between the use of beta-blockers and psychological intervention investigated in Study V. As previously mentioned, beta-blockers might interfere with exposure therapy, as anxiolytic medications can dampen the physiological arousal necessary for effective exposure (Preston et al., 2025). Although there are no clear guidelines regarding the medical treatments for these patients, beta-blockers have been associated with long-term survival for TS-patients (Raposeiras-Roubin et al., 2025; Santoro et al., 2024), and there is a trend towards lower risk of MACE for MINOCA patients (Lindahl et al., 2017). As such, it is not unlikely that these patients were taking beta-blockers during the treatment period. This could be an alternative explanation why the treatment did not seem effective in reducing symptoms on CAQ-Av, as beta-blocker treatment may have blunted the physiological arousal necessary for effective exposure therapy, potentially interfering with inhibitory learning and emotional processing.

Methodological discussion

Positivism

This dissertation is marked by the works of positivistic research, which puts an emphasis on objectivity, and generation of quantifiable data that can be replicated and generalised (Park et al., 2020). This is the dominating perspective in psychology but is also criticised and challenged as it may not have the tools to correctly describe all psychological phenomenon (Smedslund, 2016). In contrast, some researchers might emphasise interpretivist methods of qualitative research, that instead focus on describing deeper meaning and individual experiences in a certain context. While one approach cannot be considered superior to the other, they can both contribute meaningful knowledge depending on the research question. For example, Study V investigated whether ICBT had any treatment effects on symptoms of stress and anxiety and how well it treated these symptoms. Answering this question was best suited by quantitative methods. But this intervention study was based on several previous qualitative works of research (Humphries et al., 2020; Rondung et al., 2022; Sundelin et al., 2020) that described the needs of these patients and guided how to address them. When considering which parts of the intervention were more successful, which ones were not, and for whom, how, and when it was effective can to some extent be answered with quantitative methods. For whom could be answered by analysing background variables as predictors for treatment outcomes, and when could be analysed by comparing those who got immediate access to the treatment and those who got access after the waiting period. Analysing weekly ratings could also to some extent help answer what parts of the intervention that seemed more effective, or how high a dose would be necessary to identify a relevant amount of improvement. Analysing patient engagement can also provide some parametric estimations of which treatment modules were preferrable. Still, these possible analyses, while helpful, are also rigid and might miss valuable information. An integration of process evaluation (Linnan & Steckler, 2002), or process tracing (Beach, 2017) in the evaluation of the trial might have helped give more nuance to these questions, and helped inform future development and implementation.

Study design

Both Study I and II were based on data collected in the U-CARE Heart trial, that investigated the effect of ICBT for patients with a recent MI. It should be noted that these patients participated based on their willingness to undergo psychotherapy. These patients may have a different understanding or experience of anxiety – compared to those patients who are not interested in psychotherapy – which may have affected their response pattern on the CAQ. In Study I it could be argued that this questions the generalizability of the findings. However, the most appropriate factor structure very much resembled the original structure, which also has been validated in the general population (Fischer et al., 2012). A strength of Study I was still that it is the first to follow proper methodological considerations when performing factor analyses. This has added to the understanding of the CAQ and helps using it in clinical and research practice.

Furthermore, this analysis was based on CTT, which has certain limitations (Nguyen et al., 2014). Like the other questionnaires used in this dissertation, the CAQ is based on ordinal data, which is arguably not designed to support parametric calculations (Smith, 2001). However, modern test-theory (MTT) has been developed to deal with this issue, using item-response theory (IRT), with Rasch analysis being a popular choice (Da Rocha et al., 2013; Stenbeck et al., 1992). Analysing a questionnaire on the basis of MTT allows analysis on item-level and can deal with analysing ordinal data. Furthermore, these analyses may provide further insight into which items fit the scale and what properties they have (Smith, 2001).

In Study II, the fact that patients were offered psychological treatment during the follow-up might have led to differential misclassification of exposure status. An individual that was assessed at a certain level of anxiety at baseline might have participated in the treatment shortly thereafter which may have led to different level of exposure than estimated. In other words, if the treatment managed to reduce symptoms of anxiety, this would have led to an overestimation of exposed individuals and bias the results towards the null. However, publications of the U-CARE Heart trial indicate poor evidence of effectiveness (Norlund et al., 2018), and low adherence (Wallert et al., 2018), which minimise concerns regarding this potential source of bias. Still, to account for it, a sensitivity analysis was also conducted, where patients who were randomised to the treatment arm were excluded. In this analysis there was no longer any convincing evidence of an association between HADS-A and risk of recurrent MACE, but results remained otherwise unchanged. There is, however, an issue with this procedure that introduces another source of bias. All patients that were randomised to treatment had been included based on scoring >7 on either HADS subscale. Thus, removing these patients leads to an increased emphasis on patients with sub-clinical levels of anxiety or depression. It might be self-explanatory, that within this group of patients, anxiety loses its predictive power.

An important consideration regarding the design of Study III is that patients were first randomised in the main trial (REDUCE), before being asked to participate in the sub study (RQoL). Although participants were relatively well divided between the two groups (No BB, N=397; BB, N=409), this knowledge might have influenced their choice and created some unknown bias in the data. Furthermore, this design also allowed for participants to know their randomisation status before completing the baseline assessments. In the published article we report that that the patients in the beta-blocker group reported an average of 3.8 on the HADS-D compared to 4.1 in the no beta-blocker group, but that the evidence of this difference was weak (p=0.13). However, we also asked patients whether they had any expectation of adverse effects from the beta-blockers. While most patients answered that they were unsure (61%), the two randomisation groups clearly differed among those who answered yes (No BB: 18% vs BB: 8%) and no (No BB: 11% vs. BB: 22%). It is possible that an expectation effect mediated the effect of beta-blockers on depression in the short-term follow-up (W. A. Brown, 2015). According to the theory of cognitive dissonance, an individual experiences discomfort when maintaining two or more conflicting behaviours or cognitions (Festinger, 1962). For example, taking beta-blockers and thinking they are bad, or vice versa, leads to discomfort. Subsequently, the individual may attempt to escape this discomfort by changing their behaviours or cognitions. A change in behaviour could be to not take the beta-blockers if they thought they were bad, or find another way of acquiring them if they thought they were good. A change in cognition could be altering beliefs about beta-blockers, for example regarding side effects. Consequently, taking beta-blockers and believing they are good might have led to a more positive outlook on the future, thus affecting depressive symptoms. A subsiding expectation effect could thus make the patients randomised to beta-blockers less positive, relative to the baseline, and more depressed over time. These are important limitations of the study potentially biasing the results, and future studies should attempt to replicate the findings, using a proper baseline assessment (before randomisation), and placebo controls.

The appropriateness of the method of Study IV to answer the research question might be questioned. For example, including many studies with a high risk of bias and not pooling the data in a meta-analysis makes it harder to draw any easily generalizable conclusions from the findings. Initially, the plan was to conduct a meta-analysis. However, when starting the literature search it became apparent that the high heterogeneity between studies and low-quality data would not be sufficient to generate any meaningful pooled estimates. Therefore, the purpose of the review was slightly reframed as to not only present the mental health status and QoL of MINOCA- and TS-patients after the event, but also to demonstrate the quality of current evidence base on this topic. A narrative synthesis of results was therefore deemed the appropriate method of data presentation (Popay et al., 2006).

Furthermore, the statistical approach in Study IV was different compared to the other studies in this dissertation. We did not perform any new statistical analyses, except from simple descriptive statistics of the studies. However, judging whether a study had evidence of a difference was based on the hypothesis test that had been conducted in the study. Dissimilar from the other studies in this dissertation, p-values were not interpreted as a measure of the strength of evidence. However, the studies with a lower risk of bias and higher relevance were described in greater detail in the narrative synthesis, where effect sizes and 95% CIs were also presented. This helps judge both the strength of evidence of the findings, as well as the clinical relevance.

Another limitation, affecting both Study IV and V, is the developing diagnostic landscape of MINOCA and TS. For some of the studies included in Study IV, TS would have been considered a sub-category of MINOCA, as they were published before the updated definition of MI (Thygesen et al., 2018). Similarly, Study V was conceived before this update, and it is possible that MINOCA would not have been considered an inclusion criterion if it happened later. Consequently, there remains uncertainty regarding the diagnostic certainty of MINOCA and TS, which also introduces bias to any analysis trying to differentiate the two, either from each other or from other groups.

The weak evidence of an effect on the primary outcome in Study V might be explained by its definition. First, a composite outcome cannot reflect all the complexity of the underlying measure (Barclay et al., 2019). For example, a treatment could be very effective if it helped reduce symptoms on the HADS-A from 21 to 8, but it would still not meet the primary outcome considered in Study V. Second, dichotomising continuous variables also has the statistical consequence of reducing power in the analysis (MacCallum et al., 2002; Royston et al., 2006). Both of these consequences increase the risk of a type-II error, if following a hypothesis testing procedure, or weakens the strength of the evidence measured if following the significance testing procedure. This is well illustrated by the strong evidence of an effects when analysing the primary outcomes as continuous. This also very well illustrates the important distinction between statistical and clinical significance. The proportion of patients in the treatment group had a 40% higher rate of reporting subclinical levels of both stress and anxiety, compared to the control group, but the effect would not be statistically significant. A possible explanation for the lacking power in this study was that sample size calculations were made based on a follow-up at six months, instead of three months as conducted in Study V (Olsson et al., 2022).

Another limitation of Study V was the use of wait-list controls. Waiting for a treatment has been associated with small improvements in anxiety, that may bias the effect sizes when comparing treatment groups (Steinert et al., 2017). As previously mentioned, statistical evidence does not only rely on the size of the measure of strength of evidence, but also on the probability that a particular study design will generate misleading evidence (Blume, 2011). Thus, using this type of controls might have masked some of the treatment effect, and increased the risk of type II errors.

Another limitation with using wait-list controls is that it hinders making randomised comparisons after the 3-month follow-up, and makes it harder to investigate potential effects on cardiac health.

Practical implications

The major implication of this dissertation is to show the benefit of screening for symptoms of anxiety in a clinical cardiology setting. Screening results can be used to inform contact with a trained professional and to administer proper treatment to help alleviate mental distress, but potentially also improve the CV prognosis.

Most importantly, using scales that assess physiological and behavioural aspect of anxiety (e.g., HADS-A and CAQ-Av) seem to be helpful for the purpose of risk prediction.

There are also some indications for caution to physicians when prescribing beta-blockers to patients with preserved LVEF. There seem to be a slight risk for elevated symptoms of depression, especially for those patients who have been taking them for a longer time. However, as beta-blockers might be anxiolytic for those with moderately elevated levels of anxiety after an MI, this could also be considered a potential benefit. Again, screening for anxiety would be beneficial for clinical decision making. Physicians may consider this information and weigh the potential benefits and drawbacks of prescription or discontinuation of beta-blockers.

Regarding patients who recently experienced a MINOCA or TS, it seems particularly important to screen for mental health issues and offering patient-tailored psychological interventions (such as the ICBT reported on in this dissertation). Although several questions remain, this may not only improve QoL of the patients but also improve their CV prognosis and reduce health-care consumption.

Future directions

In Study I, we illustrated that the Swedish translation of CAQ has a reasonable reliability and validity. However, some limitations were highlighted. Future research should investigate whether the questionnaire could be improved, potentially by the use of MTT. Suggestions for improvement are: increase specificity for items to better capture anxiety-related behaviours and cognitions, consider whether the reassurance seeking scale should be included and if so, add more items for reliability, consider the content validity of items regarding sleep disturbance, and consider the items possibly referring to cardiac disease conviction and whether this is a valid subscale to be included in the scale.

Study II showed that anxiety symptoms were independently related to the risk of recurrent MACE in post-MI patients. It also illustrated that different aspects of anxiety related differently to risk. Focusing on different aspects of anxiety in this area of research is novel and findings need to be replicated.

Study III highlighted the possible risk of inducing depressive symptoms by taking beta-blockers. Various stratified analyses also indicated possible subgroups that might be more sensitive or have differential effects. Future studies should continue investigating for what effects beta-blockers have and for whom, for example investigating only anxious MI-patients, or differentiating by disease status. Results also need to be replicated in studies that use proper pre-randomisation assessments and placebo controls, to reduce the impact of potential bias.

Study IV indicates the need to conduct more methodologically sound, and sufficiently powered studies to arrive at a clearer conclusion regarding the mental health status and QoL of MINOCA- and TS-patients after the event. These studies should help answer more specific questions, such as if certain symptom clusters are more common after the event, and different time-varying effects, as these patients (and perhaps particularly TS-patients) may have lingering problems with mental health. Emerging findings also indicate the need to separate the two conditions, studying them separately.

Study V showed that a tailored ICBT intervention focusing on stress and anxiety was effective when treating patients after a MINOCA or TS event. However, several questions remain. The study design did not allow for a randomised follow-up regarding recurrent cardiac events, due to the wait-list controls. Future studies could retain the randomisation groups for the entire follow-up period, to allow for longer follow-up comparisons and to investigate potential effects on cardiac health. Additionally, potential predictors, mediators and moderators of treatment outcomes should be investigated, such as previous psychiatric diagnoses, personality traits, social and environmental circumstances, medication status (e.g., beta-blockers), and CV diagnosis, as indicated by the sub-group analysis.

Conclusion

By the papers included in this dissertation I have illustrated the importance of screening for anxiety in patients after an MI, MINOCA or TS. When screening for anxiety in this context, it is important to consider what specific symptoms that are of interest and how they are temporally and causally related to each other and other psychological constructs.

- The Swedish translation of the cardiac anxiety questionnaire has acceptable psychometric properties in post-MI patients, but could benefit from some revisions.
- Physiological and behavioural aspects of anxiety are related to the risk of recurrent cardiac events in post-MI patients, but cognitive and affective are not.
- Beta-blockers are associated with a slight increase of depressive symptoms in post-MI patients, with preserved LVEF. The effect on depressive symptoms was particularly pronounced in patients that were randomised to continued use, rather than first-time users. Additionally, beta-blockers had, on average, no effect on anxiety symptoms but might help reduce anxiety for those with moderately elevated symptoms.
- Patients have worse mental health and quality of life after a MINOCA or TS, compared to non-cardiac groups, and as bad or worse than cardiac groups. For some, symptoms persist or even worsen over time. Current evidence regarding these questions has a high risk of bias and more research is needed.
- A patient-tailored ICBT-programme effectively reduced symptoms of stress, anxiety and post-traumatic stress in patients after a MINOCA or TS. Exploratory findings indicate that especially TS-patients seem to derive benefit from the intervention.

These findings highlight ways in which psychological expertise could contribute and be used to benefit both psychological and somatic health patients in CV care.

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Vem är du?

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